

**MULTI-CENTER RANDOMIZED PLACEBO-CONTROLLED TRIAL OF NOCTURNAL  
OXYGEN THERAPY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE  
THE INTERNATIONAL NOCTURNAL OXYGEN (INOX) TRIAL**

**1. THE NEED FOR A TRIAL**

**1.1 WHAT IS THE PROBLEM TO BE ADDRESSED?**

Chronic obstructive pulmonary disease (COPD) represents a major health issue in Canada. Among Canadians aged  $\geq 55$ , the prevalence rate of the disease is about 6% [1-3]. About 750 000 Canadians suffer from the disease [2]. COPD represents the fourth leading cause of mortality in men aged  $\geq 65$  and the seventh in women aged  $\geq 65$  [4]. Continuous oxygen therapy (CONT-O2) is one of the few components of the management of COPD that improves survival. It is only indicated in patients with severe daytime hypoxemia (defined as an arterial oxygen pressure [PaO2] measured in stable state  $\leq 55$  mmHg or in the range of 56-59 mmHg when clinical evidence of pulmonary hypertension or polycythemia are noted) [5;6]. CONT-O2 is usually provided by a stationary oxygen concentrator, with or without an additional ambulatory module. CONT-O2 should be used for at least 15 hours a day [7].

Several studies have demonstrated oxygen desaturation during sleep in patients with COPD [8-16]. The earliest studies that described this phenomenon included patients with marked daytime hypoxemia qualifying for CONT-O2. Conventional CONT-O2, given 15-18 hours/day, compulsorily includes sleep time and therefore corrects sleep-related hypoxemia. However, sleep-related oxygen desaturation often occurs in patients not qualifying for CONT-O2. Sleep-related oxygen desaturation is considered by many physicians as an indication for providing nocturnal oxygen therapy (N-O2) in patients who would not otherwise qualify for CONT-O2. This perceived indication stems from the suggestion that the natural progression of COPD to its end stages of severe hypoxemia, right heart failure, and death may be dependent upon the severity of desaturation occurring during sleep [17-19]. This attractive hypothesis is supported by the fact that hypoxemic episodes during sleep are accompanied by increases in pulmonary arterial pressure [20-22] and often by important cardiac arrhythmias [23;24]. Supplemental nocturnal oxygen alleviates both the acute increases in pulmonary arterial pressure [20-22] and the cardiac arrhythmias [23;24]. It has been suggested that, over the long run, N-O2 may halt the progression of long-standing cor pulmonale [5;22] and may prolong survival [6]. Practice guidelines regarding the indications for N-O2 in COPD not qualifying for conventional CONT-O2 are presently imprecise. Because of this, a number of these patients are currently treated with N-O2 [25]. For instance, a recent practice review and appraisal at the Quebec City area's respiratory home care program indicated that, as of September 1<sup>st</sup> 2006, 74 of the 364 patients (20.3%) registered to the program with a primary diagnosis of COPD were receiving home oxygen for nocturnal utilization only (Appendix 1). However, the clinical benefits of N-O2 have yet to be confirmed. The International Nocturnal Oxygen (INOX) trial is intended to address this issue.

**1.2 WHAT ARE THE PRINCIPAL RESEARCH QUESTIONS TO BE ADDRESSED?**

**1.2.1 Primary question**

In patients with COPD not qualifying for CONT-O2 who exhibit significant nocturnal arterial oxygen desaturation, does N-O2 provided for a period of 3 years decrease mortality or the requirement for CONT-O2?

**1.2.2 Secondary questions**

- In the same population, does N-O2 improve disease-specific quality of life?
- What is the incremental cost-effectiveness ratio of nocturnal oxygen therapy over a 3-year period?

**1.2.3 Hypotheses**

In patients with COPD not qualifying for CONT-O2 who exhibit significant nocturnal arterial oxygen desaturation, N-O2 provided for a period of 3 years (1) is effective in decreasing mortality and the requirement for CONT-O2, (2) improves disease-specific quality of life, and (3) is cost effective.

### **1.3 WHY IS A TRIAL NEEDED NOW? EVIDENCE FROM THE MEDICAL LITERATURE**

#### **1.3.1 Continuous oxygen therapy in COPD**

##### *a) CONT-O2: Clinical aspects*

In the early 1980s, two randomized controlled trials of CONT-O2 in patients with COPD were published: the United Kingdom Medical Research Council (MRC) Study [5] and the National Heart, Lung, and Blood Institute (NHLBI)'s Nocturnal Oxygen Therapy Trial [6]. Both clearly demonstrated increased survival from low-flow domiciliary oxygen use in severely hypoxemic (daytime resting PaO<sub>2</sub> ≤ 55 mmHg) patients with COPD. The MRC study randomly assigned patients to receive 15 hours of oxygen therapy (including hours of sleep) per day vs. no oxygen therapy at all. At 5-year follow-up, the oxygen therapy group had improved survival: 19 of 42 oxygen therapy patients (42%) had died, compared to 30 of the 45 control patients (66%). The NHLBI trial randomly assigned patients to receive oxygen for either 12 hours a day (nocturnal group) or 24 hours a day (continuous group). The CONT-O2 group actually received oxygen for an average of 19 hours a day. All patients received oxygen therapy during sleep. At 24 months, the overall mortality in the CONT-O2 group was 22.4%, whereas it was 40.8% in the N-O2 group ( $p = 0.01$ ). Survival of patients in the NHLBI trial who were submitted to N-O2 was greater than survival of patients in the MRC trial who were allocated to the control group. This only provides indirect evidence that N-O2 is beneficial, at least in severely hypoxemic patients (i.e., those qualifying for CONT-O2). A more recent randomized trial indicated that CONT-O2 does not improve survival in patients with moderate hypoxemia (PaO<sub>2</sub>: 56-65 mmHg) [26].

##### *b) CONT-O2: Economic aspects*

COPD represents a significant burden on health care systems, the main cost drivers being inpatient care, medications and oxygen therapy [27-33]. This was confirmed by the recent Confronting COPD Survey [34]. In this survey, more than 200 000 households were screened by random-digit dialing in 8 countries, including Canada. In the Canadian cohort of the Confronting COPD Survey (3265 individuals; mean age: 63 years; 44% female), the annual direct cost of the disease was estimated at \$1997 per patient [35]. The economic burden of COPD was particularly high in terms of inpatient care: although only 14% of patients reported being hospitalized in the last 12 months, hospital stays accounted for over half (53%) of the total direct costs per patient. Outpatient treatment for COPD accounted for over 30% of total direct costs, and the majority of these costs was for home oxygen therapy. Overall, oxygen therapy accounted for 17% of the entire annual direct costs of COPD care.

#### **1.3.2 Nocturnal oxygen therapy in COPD**

##### *a) N-O2: Clinical aspects*

Three randomized trials directly addressed the issue of the effectiveness of N-O2 in patients not qualifying for CONT-O2 who exhibit nocturnal oxygen desaturations [36-38] (see section 1.4 *Reference to a systematic review*). Two looked at the effect of N-O2 on survival [36,37].

- The American (Fletcher's) study [36]

This randomized, double-blind, three-year trial compared N-O2 at 3 liters/minute delivered by concentrator to room air delivered by a defective concentrator ("sham concentrator"). The primary outcome of this trial consisted of pulmonary hemodynamic parameters. Survival and requirement for CONT-O2 were secondary outcomes. Thirty-eight patients were randomized. The hemodynamic data were limited to 9 sham- and 7 oxygen-treated patients. The nocturnal desaturator group who received supplemental oxygen during sleep over 36 months showed a significant downward trend in pulmonary artery pressure (-3.7 mmHg) compared with those in the control group (+ 3.9 mmHg;  $p = 0.02$ ). There was no significant difference in mortality between the oxygen- and sham-treated patients.

• The French (Chaouat's) study [37]

This open trial looked at the effectiveness of N-O<sub>2</sub> in patients with COPD with mild-to-moderate daytime hypoxemia (PaO<sub>2</sub> 56-69 mmHg) exhibiting sleep-related oxygen desaturation. Sleep-related oxygen desaturation was defined as spending  $\geq 30\%$  of the recording time with transcutaneous arterial oxygen saturation  $< 90\%$ . This definition of “nocturnal desaturation” represents the one that is the most currently accepted in Canada. The endpoints included survival, requirement for CONT-O<sub>2</sub> and pulmonary hemodynamic effects after 2 years of follow-up. Seventy-six patients were randomized; 41 were allocated to N-O<sub>2</sub> and 35 to no N-O<sub>2</sub>. Twenty-two patients (12 in the N-O<sub>2</sub> group and 10 in the control group,  $p = 0.98$ ) required CONT-O<sub>2</sub> during the follow-up period ( $35 \pm 14$  months). Sixteen patients died (9 in the N-O<sub>2</sub> group, and 7 in the control group,  $p = 0.84$ ). The changes in the mean pulmonary artery pressure in the N-O<sub>2</sub> group and the control group were not different. The authors concluded that N-O<sub>2</sub> had no effect on survival, did not allow delay in the requirement for CONT-O<sub>2</sub> and did not modify the evolution of pulmonary hemodynamics.

Table 1 is a summary of the American and the French studies. We computed the relative risks and associated 95% confidence intervals from the data reported in the respective articles. Both trials were negative. However, both were underpowered as demonstrated by the width of the confidence intervals surrounding the relative risks.

**Table 1. Summary of randomized trials of nocturnal oxygen therapy in COPD**

Trials	Outcomes	Risk with therapy	Risk without therapy	Relative risk (95% CI)
<b>Fletcher [36]</b>	• mortality	5/19	6/19	0.8 (0.3 – 2.2)
	• progression to CONT-O <sub>2</sub>	6/19	1/19	6.0 (1.1 – 36.4)
	• composite outcome*	11/19	7/19	1.6 (0.8 – 3.3)
<b>Chaouat [37]</b>	• mortality	9/41	7/35	1.1 (0.5 – 2.6)
	• progression to CONT-O <sub>2</sub>	12/41	10/35	1.0 (0.5 – 2.1)
	• composite outcome*	19/41	14/35	1.2 (0.7 – 2.0)

\* composite outcome: mortality or requirement for CONT-O<sub>2</sub>

• The German (Orth's) study [38]

In a pilot randomized, placebo-controlled cross-over trial, Orth et al. [38] investigated the influence of N-O<sub>2</sub> on quality of life in 19 daytime normoxemic COPD patients with nocturnal oxygen desaturation that was defined according to the French criteria. Each treatment period lasted 6 weeks. Mortality was not an outcome in this trial. Significant differences were observed only in the sleep dimension of the Nottingham Health Profile. All the other dimensions of the Nottingham Health Profile, SF-36 and St-George's Respiratory Questionnaire showed no difference between N-O<sub>2</sub> and placebo. The authors concluded that N-O<sub>2</sub> was not able to improve quality of life within 6 weeks after initiation of therapy.

*b) N-O<sub>2</sub>: Economic aspects*

We could not locate any economic evaluation specifically investigating the cost-effectiveness of N-O<sub>2</sub>. However, given *i*) the total Canadian population with COPD - 750 000 individuals [2], *ii*) the annual direct cost of COPD in Canada - \$1997 per patient [34], *iii*) the proportion of this budget dedicated to home oxygen therapy - 17% [34], and *iv*) the proportion of patients with COPD receiving home oxygen for nocturnal utilization only - 20% (Appendix 1), we estimate that the annual direct cost of nocturnal oxygen therapy in Canada amounts to \$51 million.

**1.3.3 Preliminary work done by the applicants to support the clinical trial**

*a) Survey and needs assessment of Canadian respirologists*

We recently conducted a mail survey of all the respirologists registered in the 2006 Canadian Medical Directory in order to characterize their perception and clinical practice regarding the indications and prescription of nocturnal oxygen therapy in COPD ([39]; Appendix 2). Another important objective

was to determine what would be considered as an important treatment effect of N-O<sub>2</sub> in a placebo-controlled randomized trial. We found that Canadian respirologists are highly interested by the issue of nocturnal oxygen desaturation in COPD. The response rate to the survey was 60%, with 99% of the respondents indicating that the problem of nocturnal oxygen desaturation is clinically relevant. The survey identified wide variations in clinical practices among physicians in several areas of the management of nocturnal oxygen desaturation (including its definition, its diagnostic modalities and the perceived indications of N-O<sub>2</sub>). The results of the survey emphasized the needs for further research.

*b) Results of a five-site pilot feasibility study*

We successfully completed a pilot study looking at the prevalence of nocturnal desaturation in a cohort of patients with COPD and moderate hypoxemia (PaO<sub>2</sub>: 56 to 69 mmHg). Its results are summarized in Appendix 3. From this pilot study of 128 patients conducted in 5 clinical sites that will participate in the INOX trial, we determined that 40% (95% CI: 31 – 49) of the patients with moderate-to-severe COPD not qualifying for CONT-O<sub>2</sub> are nocturnal oxygen desaturators.

*c) Accuracy of home oxygen oximetry to exclude obstructive sleep apnea in COPD*

Whether home nocturnal oximetry is sufficient to distinguish between sleep apnea and nocturnal oxygen desaturation alone (i.e., without sleep apnea) is debated. We studied, in a blind comparison of home nocturnal oximetry and laboratory polysomnography, consecutive patients with COPD and nocturnal oxygen desaturation (Appendix 4). We found that, in patients with significant nocturnal oxygen desaturation, home nocturnal oximetry has high negative predictive value (but poor positive predictive value) for the diagnosis of OSA. These results impact on the diagnostic strategies we propose (see section 2.5.4 *Nocturnal desaturation: operational definition and patient selection*).

*d) Utility scores in patients with oxygen-dependent COPD*

The clinical importance of CONT-O<sub>2</sub> for patients with severe COPD is unknown. We addressed this important question in a cross-sectional study of 102 patients with oxygen-dependent COPD (Appendix 5) to determine whether a prescription of CONT-O<sub>2</sub> approaches the value (i.e., utility) of death for patients with severe COPD. We administered the SF-36 to 102 patients with oxygen-dependent COPD in order to derive utility scores (SF-6D scores) [40]. We found that the prescription of CONT-O<sub>2</sub> is a critical step in the life of patients with severe COPD. The results of this study bear on the choice and appropriateness of the primary outcome of the INOX trial (see section 2.8.1 *Primary outcome*).

## **1.4 REFERENCE TO A SYSTEMATIC REVIEW**

### **1.4.1 Published and updated meta-analysis**

A meta-analysis of domiciliary oxygen in COPD was published in 2005 in the Cochrane Library [41]. Its objective was to determine the effect of domiciliary oxygen therapy on survival in patients with COPD. The studies of CONT-O<sub>2</sub> were considered separately from those of N-O<sub>2</sub>. The authors only identified the two randomized trials (Fletcher's and Chaouat's) on which we commented on in the previous section. There was no difference in mortality between the treated and the control groups. Considering mortality as the only outcome, the pooled odds ratio was 0.97 (95% CI: 0.41 – 2.31). The authors concluded that N-O<sub>2</sub> has no effect on survival, without commenting on the lack of precision of the treatment effect.

To complement this meta-analysis, we searched in January 2009 the Cochrane Airways Group Specialised Register of Trials in COPD which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (Central), Medline, Embase and CINHALL. Also, we hand-searched the 2005 to 2008 American Thoracic Society, American College of Chest Physicians and European Respiratory Society meeting abstracts. We did not uncover any additional completed or ongoing trial considering mortality or disease progression as outcomes (Appendix 6). In addition, we conducted a meta-analysis of the composite outcome (i.e., mortality or requirement for CONT-O<sub>2</sub>) from the data presented in Table 1. There was no difference between the

treated and the control groups (pooled odds ratio: 1.57 [95% CI: 0.75 – 3.26]).

#### **1.4.2 The need for a trial: conclusion**

From this review of the literature and our preliminary work, we conclude that:

- nocturnal oxygen desaturation may be a determinant in the natural progression of COPD to its end stages severe hypoxemia, right heart failure, and death;
- Most Canadian respirologists have already prescribed nocturnal oxygen to patients with COPD and isolated nocturnal oxygen desaturation. Current evidence from two randomized controlled trials and their meta-analysis does not support this prescription;
- the current utilization of N-O<sub>2</sub> in Canada is associated with annual cost that we estimated at \$51 M;
- the cost-effectiveness of N-O<sub>2</sub> remains unexplored.

These conclusions are consistent with those of two recent workshops of the NHLBI on the needs and opportunities of clinical research in COPD [42;43]. The latest workshop specifically targeted oxygen therapy in COPD [43]. Both identified N-O<sub>2</sub> as a research priority in order to inform clinical decision making with regard to home oxygen therapy.

#### **1.5 HOW WILL THE RESULTS OF THIS TRIAL BE USED?**

The results of this study will be used to inform clinical decision-making. The INOX trial will provide a definitive answer to questions regarding an intervention that has gained wide popularity among patients and prescribing physicians over the last few years without any evidence of its effectiveness. For instance, from our recent survey of Canadian respirologists, 87% of the respondents indicated that they have already prescribed nocturnal oxygen to patients with COPD and isolated nocturnal oxygen desaturation ([39]; Appendix 2). This contrasts with the opinion of the Canadian Thoracic Society that “there is currently no evidence to support the use of nocturnal oxygen to improve survival, sleep quality or quality of life in patients with isolated nocturnal desaturation” [7]. Undoubtedly, those who allocate financial resources (including governments and insurance companies) will be interested in this study.

#### **1.6 DESCRIPTION OF RISKS TO THE SAFETY OF PARTICIPANTS INVOLVED IN THE TRIAL**

Low-flow oxygen is safe [44]. Its benefits in appropriately selected individuals clearly outweigh the small risks. Elevations in PaCO<sub>2</sub> occur in some COPD patients receiving low-flow oxygen. The effect is generally small in magnitude and is not progressive in response to oxygen therapy alone. Nonmedical hazards such as fire have been described in current smokers but are unusual [45]. Current smokers will be excluded from the INOX trial. This risk does not exist in patients using “sham-concentrators”. Minor problems such as skin rash or nasal irritation are usually easily handled with topical treatments.

### **2. THE PROPOSED TRIAL**

#### **2.1 WHAT IS THE PROPOSED TRIAL DESIGN?**

A 3-year, multi-center, randomized, double-blind, placebo-controlled trial of N-O<sub>2</sub>. The primary end-point is a composite outcome made up of (1) all-cause mortality or (2) requirement for CONT-O<sub>2</sub>.

#### **2.2 WHAT ARE THE PLANNED TRIAL INTERVENTIONS?**

Patients will be randomly assigned to three years of treatment with either (1) home N-O<sub>2</sub>, or (2) sham therapy with ambient air.

##### **2.2.1 Experimental intervention group: nocturnal oxygen therapy**

N-O<sub>2</sub> will be delivered overnight from an electrically-powered oxygen concentrator (NewLife Intensity Oxygen Concentrator, AirSep Corporation, Buffalo, NY, USA). The concentrator provides a constant source of oxygen from ambient air using a molecular sieve that removes nitrogen and water from air to deliver 95% oxygen at flow rates of up to 4 liters/minute. Patients will be instructed to receive N-O<sub>2</sub> throughout the night, from the time they go to bed up to the time they get up. The flow of oxygen will be that allowing the nocturnal saturation to be > 90% for ≥ 90% of the recording time. This will be assessed by the mean of pulse oximetry during a full-night recording (test night). Oxygen will be provided via nasal catheters. *Titration procedure (Appendix 7):* We anticipate that, in about two third

of the cases, the needed oxygen flow will be 2 liters/minute. This statistic comes from a chart review of the patients with COPD receiving nocturnal oxygen therapy at the Quebec City Respiratory Home Care Program (Appendix 1). This flow will be given during a first test night. If this flow of oxygen is not enough to keep the saturation  $> 90\%$  for  $\geq 90\%$  of the recording time, then an additional test night will be needed, with the oxygen flow rate increased by 1 liter/minute per night, up to 4 liters/minute. A third night of testing will be scheduled exceptionally to patients who are prescribed 4 liters/minute. This ultimate test is to assess what is the percentage of these patients who are receiving an optimal treatment. This process will be the responsibility of study personnel whose only other involvement in the trial will be the installation of the home oxygen concentrators. Following each test night, the result of the oximetry will be transmitted to the coordinating center by e-mail for assessment by a trained technician with no other involvement in the trial. Feedbacks will be provided within 48 hours according to the decision tree provided in Appendix 7.

### **2.2.2 Control group: sham therapy with ambient air (sham concentrator)**

The patients allocated to the control group will receive ambient air delivered overnight through an electrically-powered oxygen concentrator rendered ineffective by bypassing the sieve beds. The ineffective concentrators will have the same external appearance as the effective ones, allowing the trial to be double-blinded. We have received approval by Health Canada in order to proceed with the modifications on the oxygen concentrators. *Titration procedure (Appendix 7)*: The patients in the control group will also be submitted to air flow adjustment. The results of the oximetry performed during those nights will also be sent to the coordinating center but will be disregarded. To preserve blinding, patients in the control group will be submitted to additional test oximetries, with the airflow rate increased by 1 liter/minute, up to 4 liters/minute.

### **2.3 WHAT ARE THE PROPOSED ARRANGEMENTS FOR ALLOCATING PARTICIPANTS TO TRIAL GROUPS?**

Patients will be randomized after informed consent is obtained. The randomization process will consist of a computer-generated random listing of the two treatment allocations blocked by variable blocks of four and six in alternance and stratified by site. Randomization will be through central allocation and coordinated by the Laboratoire de télématique biomédicale (LTB) of the Respiratory Health Network of the Fonds de la recherche en santé du Québec (FRSQ). A letter of agreement is included in Appendix 8. Physicians and research staff will be unaware of the treatment allocation prior to or following randomization. At the time of randomization, each patient will be provided with a site-specific study number according to the randomization schedule. The results of the randomization will only be communicated by the LTB to the individual responsible for the preparation, delivery and installation of the home concentrators and oxygen flow titration.

### **2.4 WHAT ARE THE PROPOSED METHODS FOR PROTECTING AGAINST OTHER SOURCES OF BIAS?**

#### **2.4.1 Double-blinding**

The primary outcome of our trial is a composite outcome made up of all-cause mortality or requirement for CONT-O2 (section 2.8.1 *Primary outcome*). The requirement for CONT-O2 is determined at least in part by the actions of clinicians. Although it follows strict criteria and guidelines defined in this protocol, there is conceivably potential for more aggressive surveillance (monitoring) of arterial blood gases in those in the control group, leading to an increased likelihood of prescription of CONT-O2 in this group. In this regard, a real placebo arm seems most appropriate in order to minimize biases. Therefore, this study will be double blinded.

## **2.4.2 Avoiding the threat of co-interventions**

In randomized trials in COPD, few interventions really altered disease progression and reduced mortality. CONT-O2 in patients with severe hypoxemia is one of them [5;6]. Smoking cessation also reduced mortality in patients with mild COPD [46]. Smokers will be excluded from this trial. Lung volume reduction surgery reduced mortality in highly selected patients with severe emphysema [47]. Finally, the evidence that inhaled corticosteroids reduce mortality in patients with COPD is still controversial [48;49]. Therefore, co-intervention is unlikely to distort the results of the trial. However, because of the extended follow-up period (3 years), new therapies may emerge or ongoing trials may demonstrate positive effects of currently available treatment modalities on mortality. We will monitor and record co-interventions that might arise throughout the trial period. Because clinical practice often varies across centers and new therapies are often introduced in different ways throughout centers, the randomization will be stratified by centers.

## **2.5 WHAT ARE THE PLANNED INCLUSION/EXCLUSION CRITERIA?**

### **2.5.1 Clinical settings**

This multi-center randomized trial was initiated by the Respiratory Health Network of the Fonds de la recherche en santé du Québec (FRSQ). It has also received the support of the Canadian Respiratory Clinical Research Consortium (Appendix 9) and will be conducted throughout Canada by a group of respirologists knowledgeable in the area of COPD and clinical research. This network has demonstrated its ability to conduct large trials by successfully completing an important trial of a self-management program in patients with severe COPD [50], a trial comparing 3 drug regimen in COPD [51;52], and another trial of home-based respiratory rehabilitation in COPD [53;54]. These 3 studies, all published in high-impact journals, involved respectively 191, 449 and 252 patients in 7, 27 and 10 Canadian centers, respectively. The list of co-investigators are provided in Appendix 10.

### **2.5.2 Inclusion criteria**

- Patients with a diagnosis of COPD supported by a history of past smoking and obstructive disease: FEV1 < 70% predicted, FEV1/FVC < 70% and a total lung capacity by body plethysmography > 80% predicted;
- Stable COPD at study entry, as demonstrated by (1) no acute exacerbation and (2) no change in medications for at least 6 weeks before enrollment in the trial;
- Non-smoking patients for at least 6 months before enrollment in the trial;
- Mild-to-moderate daytime hypoxemia with a resting SpO2 (room air) < 95% [86];
- Patients fulfilling the current definition of nocturnal oxygen desaturation, i.e.,  $\geq 30\%$  of the recording time with transcutaneous arterial oxygen saturation < 90% on at least one of two consecutive recordings;
- Ability to give informed consent.

### **2.5.3 Exclusion criteria**

- Patients with severe hypoxemia fulfilling the usual criteria for CONT-O2 at study entry: PaO2  $\leq 55$  mmHg; OR PaO2  $\leq 59$  mmHg with clinical evidence of at least one of the following: (1) peripheral edema (cor pulmonale); (2) hematocrit  $\geq 55\%$ ; (3) right ventricular hypertrophy (P pulmonale on ECG: 3 mm in leads II, III, aVf);
- Patients with proven sleep apnea (defined by an apnea/hypopnea index of  $\geq 15$  events/hour [55]) or suspected sleep apnea on oximetry tracings;
- Patients currently using N-O2;
- Patients with known left heart or congenital heart diseases, interstitial lung diseases, bronchiectasis as the main cause of obstructive disease, lung carcinoma, severe obesity (body mass index  $\geq 40$  kg/m<sup>2</sup>), or any other disease that could influence survival.

## **2.5.4 Nocturnal desaturation: operational definition and patient selection**

### *a) Definition of “nocturnal desaturation” using home oximetry*

Significant “nocturnal desaturation” will be defined on the home oximetry as  $\geq 30\%$  of the recording time (time in bed) with a transcutaneous arterial oxygen saturation  $< 90\%$  [37;56]. This definition is currently accepted in Europe and Canada [39;56]. Continuous nocturnal saturation (SaO<sub>2</sub>) monitoring will be obtained with the PalmSAT 2500™ oximeter only (Nonin Medical Inc., Plymouth, MN, USA). Data will be digitally recorded and downloaded to a computer with dedicated software for data interpretation which will also be based on visual inspection of the printed report. Only recordings of at least 4-hour duration will be accepted.

To be enrolled in the trial, all patients will undergo two oximetric studies [57] separated from each other by  $\leq 2$  weeks. Each oximetry recording will be classified as follows:

- Nocturnal desaturation (i.e.,  $\geq 30\%$  of the recording time with a transcutaneous arterial oxygen saturation  $< 90\%$ ) without suspicion of associated sleep apnea (i.e., steady tracing with non-periodic variation in saturation throughout sleep – typical example in Appendix 11A);
- Nocturnal desaturation (i.e.,  $\geq 30\%$  of the recording time with an arterial oxygen saturation  $< 90\%$ ) with suspicion of associated sleep apnea (i.e., cyclical changes in saturation in addition to the desaturations – typical example in Appendix 11B);
- No nocturnal desaturation (i.e.,  $< 30\%$  of the recording time with a saturation  $< 90\%$ ).

A flow diagram detailing the diagnostic procedures following the screening home oximetries is provided in Appendix 12. Patients with at least one abnormal recording demonstrating nocturnal desaturation with no suspicion of associated sleep apnea on both oximetries will be directly eligible, without further testing. This procedure is based on our finding that the recording time with an oxygen saturation  $< 90\%$  on two consecutive oximetries is highly correlated, indicating consistency in the pattern of desaturation captured on repeated recordings (Appendix 3). In order to certify uniformity in the diagnosis of nocturnal desaturation and in the detection of sleep apnea [58], all the oximetries will be reviewed at the coordinating center by a sleep specialist (Dr. F. Sériès) before randomization.

### *b) Polysomnography: do we need it in all patients?*

COPD and obstructive sleep apnea are common conditions. The combination of COPD and sleep apnea is referred to as the “overlap syndrome” [59]. A recent population-based study indicated that both conditions are not linked by common pathophysiological mechanisms, and that their association is only by chance [60]. The routine utilization of sleep studies in patients with COPD to distinguish between sleep apnea and nocturnal oxygen desaturation alone (i.e. without sleep apnea) is controversial. On one hand, the access to diagnostic facilities for patients with suspected sleep apnea in Canada is unfortunately very limited [61], and the requirement of a polysomnography for all patients in the frame of this study would be unrealistic. On the other hand, 42% of the Canadian respirologists think that all COPD patients with significant nocturnal desaturation should have a polysomnography to rule out sleep apnea [39]. In a blind comparison of home nocturnal oximetry and laboratory polysomnography in consecutive patients with COPD and nocturnal oxygen desaturation, we found that, in patients with significant nocturnal oxygen desaturation, home nocturnal oximetry has high negative predictive value for the diagnosis of OSA (Appendix 4). However, home nocturnal oximetry has a poor positive predictive value for the diagnosis of OSA. It is on the basis of this study that we constructed the algorithm for the patients’ screening and selection. In patients with an oximetry tracing suggestive of sleep apnea, patients will be excluded, unless sleep apnea is ruled out on the basis of a formal sleep study performed off-protocol. In such cases, the investigator will have to submit to the coordinating center the results of either a Type-1 or Type-2 sleep apnea evaluation study (i.e., complete laboratory or full ambulatory polysomnography, Appendix 13) confirming the absence of sleep apnea before the patient is randomized [62]. The sleep studies will all be reviewed by a sleep specialist (Dr. F. Sériès).



Sleep apnea will be defined as an apnea/hypopnea index  $\geq 15$  [55].

## **2.6 WHAT IS THE PROPOSED DURATION OF TREATMENT PERIOD?**

In the British MRC trial [5], 500 days elapsed before any effect of CONT-O2 appeared, when compared to no oxygen therapy at all. Therefore, we believe that a 2-year study would be too short since it seems unlikely that the benefit of N-O2 would appear in such a short period of time. The trial we propose would follow the patients for a period of 3 years, thus increasing the probability of clinical events in both groups. At 3-year follow-up, all patients will be offered to remain in the trial for an additional year. Those who accept will sign a new consent form applying to the extended period.

## **2.7 WHAT IS THE PROPOSED FREQUENCY AND DURATION OF FOLLOW-UP?**

Each patient will be followed-up for a period of 3 years, with regular visits (every 4 months) at his/her respective study site. The schedule of follow-up procedures is provided in Section 2.9.1. During the extended follow-up period, the same procedures as in Year 3 apply. Details regarding the outcome measurement are provided in section 2.8 and 2.13 (Compliance issues).

## **2.8 WHAT ARE THE PROPOSED PRIMARY AND SECONDARY OUTCOME MEASURES?**

### **2.8.1 Primary outcome**

a) *Composite outcome: all-cause mortality or requirement for CONT-O2*

All-cause mortality or requirement for CONT-O2 will define the composite and primary outcome. All-cause mortality is preferred over disease-specific mortality because of difficulties in classifying causes of death [63] and the lack of validity of death certificates in patients with COPD [64].

Although we realize the difficulties related to composite outcomes in clinical trials, the requirement of CONT-O2 must represent an endpoint of this trial for clinical and methodological reasons. The primary reason is that the condition of participants may deteriorate to the point that CONT-O2 is required. This situation is particularly problematic because CONT-O2 compulsorily includes sleep time (and therefore N-O2). If mortality was the only outcome, and if CONT-O2 was prescribed because of disease progression to a patient allocated to N-O2, N-O2 would then become CONT-O2 (which is of proven effectiveness in improving survival in COPD). Similarly, if CONT-O2 was prescribed in a patient allocated to the control group, it would then represent an important contamination. Both situations would represent important threats to the validity of our trial.

In addition, we understand that the choice of a composite outcome requires that its components (1) are of similar importance, (2) occur with similar frequency [65]. We provide herein data to support our view that our composite outcome is appropriate: (1) Importance: In a cross-sectional study, we derived utility scores (SF-6D scores) [40] in 102 patients with oxygen-dependent COPD (Appendix 5). The mean utility score was 0.60 (SD: 0.11). For comparison, this utility score is worse than that attached to a large myocardial infarction, stroke leaving permanent moderate deficit, or dissecting or ruptured aortic aneurysm, three conditions considered in the cardiovascular literature as appropriate in composite outcomes that include mortality [66]. (2) Frequency: Typical patients with COPD not qualifying for CONT-O2 who desaturate during sleep have, on average, an FEV1 35-40% predicted [15]. These patients have a 3-year mortality of 20% [37]. The rate of prescription of CONT-O2 in patients with significant nocturnal oxygen desaturation is similar to this mortality rate. In the French trial [37], 29% were prescribed CONT-O2 during the study period; 40% reached one or the other of the endpoints.

b) *Criteria for CONT-O2 and initiation of CONT-O2*

The widely accepted criteria for CONT-O2 derived from the NHLBI's Nocturnal Oxygen Therapy Trial [6] will be used (see section 2.5.3 *Exclusion criteria*). These criteria are always met in either of the two following clinical circumstances:

- In stable patients (> 45 days from an acute exacerbation of COPD; Appendix 14A):
- Patients may become severely hypoxemic over time, following a slow decline in lung function that characterizes the natural course of the disease. In such circumstances, the requirement for CONT-O2 is

captured through periodic surveillance. At each protocol-based follow-up visit, patients will be submitted to pulse oximetry at rest using a PalmSAT 2500™ oximeter (Nonin Medical, Inc. Plymouth, MN, USA) that estimates arterial saturation in oxygen with a precision of  $\pm 2\%$ . The criteria for CONT-O2 requirement defined in section 2.8.1.b correspond to a saturation  $< 90\%$ . If pulse oximetry at rest gives a saturation  $\geq 92\%$ , then direct arterial blood gas measurement is not required. Otherwise, arterial blood gas must be sampled for direct PaO2 measurement. Patients whose PaO2 falls below 56 mmHg during the follow-up period may be given conventional CONT-O2. The trial end-point will then be reached. Vital status will also be determined at 3 years for all the participants.

- In unstable patients ( $\leq 45$  days following an acute exacerbation of COPD; Appendix 14B):

Patients may become severely but temporarily hypoxemic during an acute exacerbation of COPD necessitating hospitalization. In such circumstances, oxygen therapy may be prescribed for a short period of time, especially if the oxygen therapy allows the patient to be safely discharged from the hospital sooner [67]. Any decision regarding the maintenance of oxygen therapy (i.e., the requirement of CONT-O2 following short-term oxygen therapy) must be made after a period of clinical stability of at least 30 days [67]. Reevaluation must occur within 12 weeks after the end of the treatment of the exacerbation. The primary endpoint will be considered to be reached only when CONT-O2 criteria are met. Vital status will be determined at 3 years for all the participants.

Details regarding the prescription procedures in such circumstance are provided in section 2.9.2.

## 2.8.2 Secondary outcomes

The secondary outcomes are described in section 2.10.

## 2.9 HOW WILL THE OUTCOME MEASURES BE MEASURED AT FOLLOW-UP?

### 2.9.1 Baseline evaluation and protocol-based follow-up visits (Table 2 and 2.1)

The usual socio-demographic and clinical characteristics will be obtained at baseline. Spirometry will be performed according to the American Thoracic Society requirements [68], lung volumes measurement by plethysmography [69], and carbon monoxide diffusion capacity measurement by the single-breath method [70]. All arterial blood gases will be measured while breathing at room air. In case of death, the date at which the primary outcome is reached will be obtained directly from chart review, contact with the treating physician or on the basis of interviews with surviving relatives during the protocol-based home visits or telephone interviews.

**Table 2. Schedule of follow-up procedures**

FLOW CHART	0	4 m	8 m	1 yr	16 m	20 m	2 yrs	28 m	32 m	3 yrs
Core questionnaire + spiro	√			√			√			√
Arterial blood gas	√	(√) <sup>1</sup>	(√) <sup>1</sup>	√	(√) <sup>1</sup>	(√) <sup>1</sup>	√	(√) <sup>1</sup>	(√) <sup>1</sup>	√
Stipends	√	√	√	√	√	√	√	√	√	√
PFT (Plethysmography)	√			√			√			√
Pulse oxymetry		√	√		√	√		√	√	
Quality of life questionnaires	√			√			√			√
Health Care qst (fup call or visit) <sup>2</sup>		√√	√√	√√	√√	√√	√√	√√	√√	√√
Home visits for compliance <sup>3</sup>		√	√	√	√	√	√	√	√	√
2 nights of nocturnal oxymetry	√									
Baseline information form	√									
Consent form(s)	√									

<sup>1</sup>Depending on the result of the arterial saturation in oxygen measured by pulse oximetry.

<sup>2</sup>Health care utilization will be measured through telephone contacts with patients every two months (see section 2.10.3).

<sup>3</sup>Home visits will be performed by home care service provider staff and payments will be done from the INOX coordinating centre.

Patients who accept to proceed with a 4<sup>th</sup> year of follow-up, the same procedures as in Year 3 will apply in Year 4 (Month 28 = Month 40, Month 32 = Month 44, and Month 36 = Month 48).

**Table 2.1 Schedule of the extended follow-up at Year 4**

FLOW CHART	40 m	44 m	4 yr
Core questionnaire + spiro			√
Arterial blood gas	(√) <sup>1</sup>	(√) <sup>1</sup>	√
Stipends	√	√	√
PFT (Plethysmography)			√
Pulse oxymetry	√	√	
Quality of life questionnaires			√
Health Care qst (fup call or visit) <sup>2</sup>	√√	√√	√√
Home visits for compliance <sup>3</sup>	√	√	√

<sup>1</sup>Depending on the result of the arterial saturation in oxygen measured by pulse oximetry.

<sup>2</sup>Health care utilization will be measured through telephone contacts with patients every two months (see section 2.10.3).

<sup>3</sup>Home visits will be performed by home care service provider staff and payments will be done from the INOX coordinating centre.

## 2.9.2 Procedures during acute exacerbations of COPD necessitating oxygen therapy

### a) Definition and treatment

An exacerbation of COPD will be defined as a new respiratory event of complication prompting patient evaluation and initiation of additional treatment regimens (including antibiotics and/or systemic steroids) in an office or emergency department [71]. The evaluation plan and treatment at the onset of an exacerbation will be the responsibility of the treating physician. No restriction on the treatment regimen during the exacerbation will be imposed.

### b) Assessment of oxygen requirement during and following an exacerbation (Appendix 14B)

During an exacerbation prompting medical evaluation, arterial oxygen saturation measurement by pulse oximetry is part of the routine assessment. Patients may then be found to be severely hypoxemic. Home oxygen therapy may then be prescribed for a short period of time (usually 4 to 6 weeks). In such circumstances, this prescription of oxygen is not definitive. The indication of home oxygen must be reassessed. If short-term oxygen therapy is prescribed following an acute exacerbation, the patient is reevaluated after a period of clinical stability of at least 30 days (and no more than 90 days). If the patient still meets the criteria for CONT-O2 defined in section 2.5.2, CONT-O2 is then prescribed. This prescription is then permanent and the trial endpoint is reached. Otherwise, oxygen therapy is stopped and the patient is not considered oxygen-dependent. The trial endpoint is not reached.

## 2.10 WILL HEALTH SERVICE RESEARCH ISSUES BE ADDRESSED?

### 2.10.1 Disease-specific quality of life: St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a disease-specific questionnaire that has been extensively validated in patients with all grades of respiratory diseases including advanced COPD [72]. The questionnaire consists of 76 items divided into three domains (symptoms, activity, and impact). Scores range from zero (perfect health) to 100 (worst possible) for each component. A change in score of 4 units is clinically significant [73;74].

### 2.10.2 Generic quality of life and utility measure: SF-36

The SF-36 is a generic questionnaire that measures 8 dimensions of health: physical functioning, role limitation due to physical problems, role limitation due to emotional problems, social functioning, mental health, energy/vitality, bodily pain and general health perceptions [75;76]. In order to use the SF-36

information in a cost/utility analysis, the SF-36 scores will be converted to a single « preference-based » utility score indicating the value that would be given to their health state by the general population. This will be done by extracting the appropriate SF-36 responses and using them to complete a 6-item health state classification, the SF-6D [40]. The SF-6D utility score will be combined to produce quality-adjusted life years (QALYs). The product of the SF-6D score at 3-year follow-up (or the latest SF-6D score recorded at the time the primary outcome of the trial is reached) and the duration of life up to 3 years will give the QALYs produced for each patient.

### **2.10.3 Comorbidity: Charlson Index**

The Charlson index is a validated one page questionnaire developed to assess comorbidities and their impact on prognosis in longitudinal studies [ 87 ] .

### **2.10.4 Health economics: costs and health care utilization**

The estimates of the cost of COPD treatment for the two intervention groups will be based on the utilization of the intervention resources during the study period. The social and health care perspectives will be adopted. The resources and the cost estimate sources are the following:

- professional time: the time required for intervention activities will be recorded by the study professionals. This will include time required for material maintenance, patients' education, and home follow-up visits. Professional costs for each patient will then be calculated by multiplying the time associated with the patient's treatment by the hourly remuneration of the appropriate professional.
- intervention materials: cost of durable materials associated with the intervention will be based on the market price, the expected economic life, and an appropriate discount rate.
- health care utilization: health care utilization will be collected by a questionnaire administered by telephone every two months (Appendix 15). We have adapted a questionnaire developed by the Respiratory Health Network of the FRSQ that was used in a prospective cohort study of patients with COPD in Quebec. Physician visit costs will be estimated by province-specific remuneration plans. For non-physician services, we will obtain costs from professional associations. Hospital inpatient costs will be estimated by province-specific indices of health resource intensity. For medication, we will use the price given on the list of drugs reimbursed through province-specific drug insurance programs. For specific analysis on costs related to utilization of health care services we will build a model with the use of the data extracted from the RAMQ and the MED-ECHO provincial databases with the consent of the subjects from the province of Quebec.

## **2.11 WHAT IS THE PROPOSED SAMPLE SIZE?**

### **2.11.1 Sample size calculation**

Typical patient with COPD not qualifying for CONT-O2 who desaturate during sleep have, on average, an FEV1 35-40% predicted [15]. In their randomized trial, the French group reported a 3-year mortality of 20% [37]. These figures are consistent with the survival rate of patients with COPD reported in the literature [77], including a large North American study (n = 985) [78]. In this study, the mean FEV1 was 36% of predicted and the average follow-up, 35 months; mortality was 23%. Mortality rates are similar to the rate of prescription of CONT-O2. In addition, in the French study [37], 29% were prescribed CONT-O2 during the study period; 40% reached one or the other of the endpoints. Therefore, we anticipate the 3-year event rate (i.e., mortality or requirement for CONT-O2) among patients not receiving N-O2 to be around 40%. In terms of planning, we are targeting a 30% relative reduction in this in the experimental group (i.e., an event rate in the control group of 40% and an event rate of 28% in the N-O2 group, or an absolute difference in event rates of 12%). This absolute difference is consistent with the minimal clinically important difference elicited by Canadian respirologists in our national survey (14%; Appendix 2). The level of statistical significance is set at  $p = 0.05$  (two-sided). Translating this in terms of our proposed log rank test (section 2.16.1), we calculated that 300 patients per group (total sample size: 600) will provide us with a power of 90%

[79]. We will enrol a total of 630 patients to account for potential consent withdrawal. Sample size issues are further discussed in Appendix 16.

### **2.11.2 Feasibility: results of a five-site pilot feasibility study**

The results of our pilot study (section 1.3.3b and Appendix 3) also carry information on the number of patients we need to screen in order to reach the target sample size of 630 patients. Given that 40% of the patients with moderate-to-severe COPD not qualifying for CONT-O2 exhibit nocturnal oxygen desaturation, 1575 will have to be screened in order to identify these 630 eligible individuals. In our survey of Canadian respirologists, we found that, on average, 30% of the respondents' practice (including that of our co-investigators) is dedicated to the care of patients with COPD (Appendix 2). This information clearly demonstrates that nocturnal oxygen desaturation in patients with COPD is not a rare occurrence and that the investigators have access to a large pool of potentially eligible patients.

### **2.12 WHAT IS THE PLANNED RECRUITMENT RATE?**

We anticipate that the recruitment will be completed within 4 years. Twenty-seven centers with specific facilities and expertise have already agreed to participate in the trial (Appendix 10). A realistic objective is to enroll 25 patients in each centre during the recruitment period.

### **2.13 ON WHAT EVIDENCE ARE THE COMPLIANCE FIGURES BASED?**

Objective daily duration of oxygen use through the concentrator during each treatment period will be measured using the concentrators' counter clock recording the number of hours of utilization. This information will be recorded by a respiratory therapist during regular home visits scheduled every 4 months. The home visits for all the participating sites will be done by respiratory therapists from the home care company, hired by the INOX coordinating centre. Patients who have used their N-O2 or sham therapy during at least 70% of the total time in bed over the 3-year trial will be judged to have been compliant. Total time in bed will be estimated from the typical daily time in bed self-reported at baseline. Patients who are non-compliant will be included in the primary intention-to-treat analysis.

### **2.14 WHAT IS THE LIKELY RATE OF LOSS TO FOLLOW-UP?**

In case of withdrawal, we will attempt to ascertain the primary outcome through review of death certificates from provincial statistics registries and chart review to determine whether the patient has been placed on CONT-O2 therapy. We anticipate the rate of loss to follow-up or consent withdrawal to be less than 5%. The total sample size will be augmented accordingly to 630.

### **2.15 HOW MANY CENTERS WILL BE INVOLVED?**

Twenty-seven centers agreed to participate in the INOX trial (Appendix 10).

### **2.16 WHAT IS THE PROPOSED TYPE OF ANALYSES?**

#### **2.16.1 Statistical analysis**

The primary analysis will follow an intent-to-treat approach. The distribution of time to achievement of the primary composite outcome (all-cause mortality or requirement for CONT-O2) will be estimated by the Kaplan-Meier method, and the difference between the two study groups will be evaluated with a log-rank test. The estimated relative risk of mortality or requirement for CONT-O2 with its 95% confidence interval will be computed. Multivariable analyses with the Cox proportional-hazards model will be used to estimate the simultaneous effects of prognostic factors (including gender, age, FEV1, and comorbidities) and on the composite outcome. Differences will be considered to be statistically significant at the 0.05 level. All statistical tests will be two-sided. The analyses for changes in quality-of-life measures will follow a similar approach: they will be based on an intention to treat approach and simple initial analyses will be followed by multivariable adjusted analyses. Although we anticipate minimal loss to follow-up, the effect of loss to follow-up will be explored through the use of a variety of imputation strategies, including multiple imputation to examine the robustness of our findings, and any conclusions that vary substantively will be clearly identified.

### **2.16.2 Economic issues: cost effectiveness analysis**

An incremental cost effectiveness analysis will be undertaken to assess the efficiency of nocturnal oxygen therapy. The overall costs and effects of the two groups will be used to calculate incremental cost effectiveness ratios according to the following equation:  $R = (C_T - C_C) / (E_T - E_C) = \Delta C / \Delta E$ , where  $R$  is the incremental cost effectiveness ratio,  $C_C$  and  $E_C$  are the means of the control group costs and effect, respectively,  $C_T$  and  $E_T$  are the means of the treatment group costs and effect, respectively, and  $\Delta C$  and  $\Delta E$  are the incremental cost and incremental effect, respectively [80]. Protocol-specific costs will be disregarded in the control group. The effect of therapy will be defined in terms of mortality, life-years and utility (section 2.10.2). Univariate and multivariable sensitivity analyses will be conducted to test the robustness of the results. Non parametric analyses (i.e., bootstrapping) will be used to derive confidence intervals for the incremental cost effectiveness ratios [81]. Although there is no accepted standard for what constitutes good value, benchmarks against which the average comparative cost-effectiveness ratios of N-O2 will be measured are available [82].

### **2.17 WHAT IS THE PROPOSED FREQUENCY OF ANALYSES? (INTERIM ANALYSIS)**

One interim analysis for efficacy will be conducted. All analyses will be run blindly and reported as such to the Data Monitoring Committee (DMC). At the interim analysis, the decision to stop or continue the trial will be made according to the DMC's charter that we developed according to the DAMOCLES Study Group's recommendations ([83]; Appendix 17). The suggested stopping rules (Haybittle-Peto procedure [84;85]) will be subject to approval by the DMC during its first meeting.

### **2.18 ARE THERE ANY PLANNED SUBGROUP ANALYSES?**

The following *a priori* hypothesis will be explored: the effect of N-O2 depends on the severity of nocturnal desaturation which may be defined in terms of % of time in bed with a saturation < 90% or in terms of mean saturation throughout the recording time (see section 2.5.4). In addition to the traditional threshold of 30% of the time with a saturation < 90%, the effect of N-O2 will be analyzed according to various thresholds of desaturation.

### **2.19 HAS ANY PILOT STUDY BEEN CARRIED OUT USING THIS DESIGN?**

We have not conducted any pilot study using this design. However, the French trial (Chaouat et al. [37]) is a clear demonstration that a randomized trial of N-O2 is feasible.

## **3. TRIAL MANAGEMENT**

### **3.1 DAY-TO-DAY MANAGEMENT**

The Coordinating Centre (Hôpital Laval, Quebec City) will provide central guidance and support to participating centers for protocol adherence. Copies of the data collection forms with information on the eligibility criteria will be sent to the Coordinating Centre before randomization (see section 2.3). Supporting documentation of the primary outcome will be forwarded no later than six weeks after occurrence or at the end of the trial if the primary outcome was not reached. Data management will be centralized at the Coordinating Centre. The Executive Committee (i.e., the principal investigator [YL], Dr. François Maltais and the study coordinator) will develop or modify all policies regarding the daily operations of the trial. It reports all safety concerns to the Steering Committee and the DMC.

### **3.2 ROLE OF PRINCIPAL APPLICANT AND CO-APPLICANTS**

The principal applicant sits on the Executive committee (section 3.1). In addition, the principal applicant and the co-applicants are all members of the Steering Committee (section 3.3).

### **3.3 STEERING AND DATA MONITORING COMMITTEES**

The Steering Committee is responsible for the design, execution, analysis and publication of results of the trial. Specific terms include (1) ratification of all major policy changes made by the Executive Committee; (2) review of all potential safety problems encountered by the Executive Committee; (3) review of accrual patterns; (4) review of randomization and data collection procedures as required. (5) discussion of any other concerns of any member of the Committee.

---

The draft DMC's charter is provided in Appendix 17. The members of the DMC are Dr. James Brophy (Cardiology and Clinical epidemiology, McGill University), Dr. Nick Anthonisen (Respiratory medicine, University of Manitoba), and Dr. Robin Roberts (Biostatistics, McMaster University).

---

REFERENCE LIST

1. Health Canada. Respiratory disease in Canada. 2001. Ottawa, Health Canada. ISBA 0-662-86-162-0. H39-593/2001F.
2. Lacasse Y, Brooks D, Goldstein RS. Trends in the epidemiology of chronic obstructive pulmonary disease in Canada, 1980-95. *Chest* 1999; 116: 306-313.
3. Chen Y, Breithaupt K, Muhajarine N. Occurrence of chronic obstructive pulmonary disease among Canadians and sex-related risk factors. *J Clin Epidemiol* 2000; 53: 755-761.
4. Stokes J, Lindsay J. Major causes of death and hospitalization in Canadian seniors. *Chron Dis Can* 1996; 17: 63-73.
5. Medical Research Council Party. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981; i: 681-686.
6. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980; 93: 391-398.
7. O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease--2007 update. *Can Respir J* 2007; 14 Suppl B: 5B-32B.
8. Leitch AG, Clancy LJ, Leggett RJ, et al. Arterial blood gas tensions, hydrogen ion, and electroencephalogram during sleep in patients with chronic ventilatory failure. *Thorax* 1976; 31: 730-735.
9. Wynne JW, Block AJ, Hemenway J, et al. Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). *Am J Med* 1979; 66: 573-579.
10. Fleetham JA, Mezon B, West P, et al. Chemical control of ventilation and sleep arterial oxygen desaturation in patients with COPD. *Am Rev Respir Dis* 1980; 122: 583-589.
11. Calverley PM, Brezinova V, Douglas NJ, et al. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. *Am Rev Respir Dis* 1982; 126: 206-210.
12. Catterall JR, Douglas NJ, Calverley PM, et al. Transient hypoxemia during sleep in chronic obstructive pulmonary disease is not a sleep apnea syndrome. *Am Rev Respir Dis* 1983; 128: 24-29.
13. Tatsumi K, Kimura H, Kunitomo F, et al. Sleep arterial oxygen desaturation and chemical control of breathing during wakefulness in COPD. *Chest* 1986; 90: 68-73.
14. Fletcher EC, Scott D, Qian W, et al. Evolution of nocturnal oxyhemoglobin desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO<sub>2</sub> above 60 mm Hg. *Am Rev Respir Dis* 1991; 144: 401-405.
15. Chaouat A, Weitzenblum E, Kessler R, et al. Sleep-related O<sub>2</sub> desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. *Eur Respir J* 1997; 10: 1730-1735.
16. Phillipson EA, Goldstein RS. Breathing during sleep in chronic obstructive pulmonary disease. State of the art. *Chest* 1984; 85: 24S-30S.
17. Flenley DC. Clinical hypoxia: Causes, consequences, and correction. *Lancet* 1978; 1: 542-546.
18. Block AJ, Boysen PG, Wynne JW. The origins of cor pulmonale; a hypothesis. *Chest* 1979; 75: 109-110.
19. Sergi M, Rizzi M, Andreoli A, et al. Are COPD patients with nocturnal REM sleep-related desaturations more prone to developing chronic respiratory failure requiring long-term oxygen therapy? *Respiration* 2002; 69: 117-122.
20. Boysen PG, Block AJ, Wynne JW, et al. Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Chest* 1979; 76: 536-542.



21. Weitzenblum E, Muzet A, Ehrhart M, et al. Variations nocturnes des gaz du sang et de la pression artérielle pulmonaire chez les bronchitiques chroniques insuffisants respiratoires. *Nouv Presse Med* 1982; 11: 1119-1122.
22. Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. The effect of short- and long-term oxygen. *Chest* 1984; 85: 6-14.
23. Flick MR, Block AJ. Nocturnal vs diurnal cardiac arrhythmias in patients with chronic obstructive pulmonary disease. *Chest* 1979; 75: 8-11.
24. Tirlapur VG, Mir MA. Nocturnal hypoxemia and associated electrocardiographic changes in patients with chronic obstructive airways disease. *N Engl J Med* 1982; 306: 125-130.
25. Wijkstra PJ, Guyatt GH, Ambrosino N, et al. International approaches to the prescription of long-term oxygen therapy. *Eur Respir J* 2001; 18: 909-913.
26. Gorecka D, Gorzelak K, Sliwinski P, et al. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; 52: 674-679.
27. Ruchlin HS, Dasbach EJ. An economic overview of chronic obstructive pulmonary disease. *Pharmacoeconomics* 2001; 19: 623-642.
28. Wilson L, Devine EB, So K. Direct medical costs of chronic obstructive pulmonary disease: chronic bronchitis and emphysema. *Respir Med* 2000; 94: 204-213.
29. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. *Chest* 2000; 117: 5S-9S.
30. Ward MM, Javitz HS, Smith WM, et al. Direct medical cost of chronic obstructive pulmonary disease in the U.S.A. *Respir Med* 2000; 94: 1123-1129.
31. Guest JF. The annual cost of chronic obstructive pulmonary disease to the UK's national health service. *Dis Manage Health Outcomes* 1999; 5: 93-100.
32. Rutten-van Molken MP, Postma MJ, Joore MA, et al. Current and future medical costs of asthma and chronic obstructive pulmonary disease in The Netherlands. *Respir Med* 1999; 93: 779-787.
33. Jacobson L, Hertzman P, Lofdahl CG, et al. The economic impact of asthma and chronic obstructive pulmonary disease (COPD) in Sweden in 1980 and 1991. *Respir Med* 2000; 94: 247-255.
34. Rennard S, Decramer M, Calverley PM, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J* 2002; 20: 799-805.
35. Chapman KR, Bourbeau J, Rance L. The burden of COPD in Canada: results from the Confronting COPD survey. *Respir Med* 2003; 97 Suppl C: S23-S31.
36. Fletcher EC, Luckett RA, Goodnight-White S, et al. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO<sub>2</sub> above 60 mm Hg. *Am Rev Respir Dis* 1992; 145: 1070-1076.
37. Chaouat A, Weitzenblum E, Kessler R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. *Eur Respir J* 1999; 14: 1002-1008.
38. Orth M, Walther JW, Yalzin S, et al. [Influence of nocturnal oxygen therapy on quality of life in patients with COPD and isolated sleep-related hypoxemia: a prospective, placebo-controlled cross-over trial]. *Pneumologie* 2008; 62: 11-16.
39. Lacasse Y, Sériès F, Martin S, et al. Nocturnal oxygen therapy in patients with COPD: A survey of Canadian respirologists. *Can Respir J* 2007; 14: 343-348.
40. Brazier J, Usherwood T, Harper R, et al. Deriving a preference-based single index from the UK SF-36 Health Survey. *J Clin Epidemiol* 1998; 51: 1115-1128.
41. Cranston JM, Crockett AJ, Moss JR, et al. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 19: CD001744.

42. Croxton TL, Weinmann GG, Senior RM, et al. Clinical research in chronic obstructive pulmonary disease: needs and opportunities. *Am J Respir Crit Care Med* 2003; 167: 1142-1149.
43. Croxton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research: an NHLBI workshop report. *Am J Respir Crit Care Med* 2006; 174: 373-378.
44. Benditt JO. Adverse effects of low-flow oxygen therapy. *Respir Care* 2000; 45: 54-61.
45. Lacasse Y, LaForge J, Maltais F. Got a match? Home oxygen therapy in current smokers. *Thorax* 2006; 61: 374-375.
46. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; 142: 233-239.
47. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059-2073.
48. Sin DD, Wu L, Anderson JA, et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 992-997.
49. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775-789.
50. Bourbeau J, Julien M, Maltais F, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003; 163: 585-591.
51. Aaron SD, Vandemheen K, Fergusson D, et al. The Canadian Optimal Therapy of COPD Trial: design, organization and patient recruitment. *Can Respir J* 2004; 11: 581-585.
52. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; 146: 545-555.
53. Maltais F, Bourbeau J, Lacasse Y, et al. A Canadian, multicentre, randomized clinical trial of home-based pulmonary rehabilitation in chronic obstructive pulmonary disease: rationale and methods. *Can Respir J* 2005; 12: 193-198.
54. Maltais F, Bourbeau J, Shapiro S, et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008; 149: 869-878.
55. Hosselet J, Ayappa I, Norman RG, et al. Classification of sleep-disordered breathing. *Am J Respir Crit Care Med* 2001; 163: 398-405.
56. Levi-Valensi P, Weitzenblum E, Rida Z, et al. Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients. *Eur Respir J* 1992; 5: 301-307.
57. Lewis CA, Eaton TE, Fergusson W, et al. Home overnight pulse oximetry in patients with COPD: more than one recording may be needed. *Chest* 2003; 123: 1127-1133.
58. Ramsey R, Mehra R, Strohl KP. Variations in physician interpretation of overnight pulse oximetry monitoring. *Chest* 2007; 132: 852-859.
59. Flenley DC. Sleep in chronic obstructive lung disease. *Clin Chest Med* 1985; 6: 651-661.
60. Bednarek M, Plywaczewski R, Jonczak L, et al. There is no relationship between chronic obstructive pulmonary disease and obstructive sleep apnea syndrome: a population study. *Respiration* 2005; 72: 142-149.
61. Flemons WW, Douglas NJ, Kuna ST, et al. Access to diagnosis and treatment of patients with suspected sleep apnea. *Am J Respir Crit Care Med* 2004; 169: 668-672.
62. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; 22: 667-689.

63. Jensen HH, Godtfredsen NS, Lange P, et al. Potential misclassification of causes of death from COPD. *Eur Respir J* 2006; 28: 781-785.
64. Ernst P, Bourbeau J, Rainville B, et al. Underestimation of COPD as a cause of death [abstract]. *Eur Respir J* 2000; 16: 13S.
65. Montori VM, Permyer-Miralda G, Ferreira-Gonzalez I, et al. Validity of composite end points in clinical trials. *BMJ* 2005; 330: 594-596.
66. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *BMJ* 2007; 334: 786.
67. Neff TA, Conway WA, Lakshminarayan S, et al. ACCP-NHLBI National Conference on Oxygen Therapy. 2. Indications for oxygen therapy. *Chest* 1984; 86: 239-240.
68. American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: 1107-1136.
69. Quanjer PhH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows: official statement of the European Respiratory Society. *Eur Respir J* 1993; [suppl. 16]: 5-40.
70. American Thoracic Society. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique--1995 update. *Am J Respir Crit Care Med* 1995; 152: 2185-2198.
71. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: S77-121.
72. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321-1327.
73. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; 19: 398-404.
74. Schunemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. *J Clin Epidemiol* 2003; 56: 1170-1176.
75. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-483.
76. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; 31: 247-263.
77. Nishimura K, Tsukino M. Clinical course and prognosis of patients with chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2000; 6: 127-132.
78. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14-20.
79. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. *Control Clin Trials* 1981; 2: 93-113.
80. Griffiths TL, Phillips CJ, Davies S, et al. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001; 56: 779-784.
81. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstrap: a non-parametric approach to confidence interval estimation. *Health Econ* 1997; 6: 327-340.
82. Institute for Clinical Research and Health Policy Studies. Center for the Evaluation of Value and Risk in Health. <http://www.nemc.org/icrhrs/resprog/cevr/default.asp> . 2006. 12-11-2006.

- 
83. DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005; 365: 711-722.
  84. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971; 44: 793-797.
  85. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; 34: 585-612.
  86. Lewis CA, Fergusson W, Eaton T, Zeng I, Kolbe J. Isolated nocturnal desaturation in COPD : prevalence and impact on quality of life and sleep. *Thorax*, 2009; 64 (2): 133-138. PMID 18390630
  87. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies : development and validation. *J Chron Dis*, 1987; 40 (5);373-383.

## APPENDIX 1

### HOME OXYGEN THERAPY IN COPD AT THE QUEBEC CITY AREA RESPIRATORY HOME CARE PROGRAM: RESULTS OF A PRACTICE REVIEW AND APPRAISAL

**Laurence Beaulieu-Genest, Sylvie Martin MSc, Yves Lacasse MD, MSc.** *Centre de recherche, Centre de Pneumologie, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie de l'Université Laval, Québec, Canada.*

**Background :** Sleep-related oxygen desaturation is considered by many physicians as an indication of providing nocturnal oxygen therapy in patients with severe chronic obstructive pulmonary disease (COPD) who would not otherwise qualify for continuous oxygen therapy (i.e., oxygen therapy provided for at least 15-18 hours a day). Although current evidence from two randomized controlled trials does not support its prescription, nocturnal oxygen therapy is covered by the Quebec medical insurance program. The proportion of patients with COPD receiving home oxygen for nocturnal utilization only is unknown.

**Objectives:** (1) To determine, among the patients with a primary diagnosis of COPD receiving oxygen therapy through a specialized respiratory home care program, the proportion of patients on nocturnal oxygen therapy only vs. those on continuous oxygen therapy; (2) to investigate the appropriateness of home oxygen prescriptions.

**Methods:** This study took place at the Quebec City area's respiratory home care program. This program is funded by the Quebec universal medical insurance plan and delivers home care (mainly home oxygen therapy and related services) to registered patients with any chronic lung disease. We reviewed the chart of all patients with a primary diagnosis of COPD registered to the program as of September 1<sup>st</sup> 2006. The following information was extracted: (1) clinical characteristics, including gender, age, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and the date of prescription of oxygen therapy; (2) whether the patients was receiving at the time of the study nocturnal oxygen therapy alone or continuous oxygen therapy. For those on nocturnal oxygen therapy alone, we noted the results of the nocturnal pulse oximetry that lead to this prescription, and whether nocturnal oxygen therapy was preceded by a course of continuous oxygen therapy. For those on continuous oxygen therapy, we noted the results of the arterial blood gas that lead to this prescription, the clinical circumstances in which oxygen therapy was initiated (e.g., following an exacerbation of COPD or following a slow decline in lung function that characterizes the natural course of the disease), and whether continuous oxygen therapy was preceded by a course of nocturnal oxygen therapy.

**Results:** As of September 1<sup>st</sup> 2006, 364 patients with a primary diagnosis of COPD were receiving oxygen therapy through our respiratory home care program. 74 (20%) were receiving home oxygen for nocturnal utilization only; the other 290 patients were on continuous oxygen therapy. Table 1 compares the clinical characteristics of the patients on continuous oxygen therapy vs. those on nocturnal oxygen therapy. On average, patients on CONT-O2 had more severe disease than those on N-O2.

Continuous oxygen therapy (n = 290): Information on the initiation of continuous oxygen therapy was available in 278 of the 290 patients (96%). Continuous oxygen therapy was initiated in the course of an acute exacerbation of COPD in 189 (68%) of them and was preceded by a course of nocturnal oxygen therapy in 19%. Following the initial prescription, the indication of continuous oxygen therapy was ascertained during a follow-up visit in 152 of these 189 patients (80%). This reevaluation took place 61 days (median) following the initial prescription. Upon reevaluation, mean pO<sub>2</sub> was 51 mmHg (SD: 5) and the mean pCO<sub>2</sub> was 50 mmHg (SD: 9 mmHg). The prescription of continuous oxygen therapy was inappropriate (i.e., pO<sub>2</sub> ≥ 60 mmHg) in 5 of the 269 patients (2%) for whom baseline arterial pO<sub>2</sub> was available.

*Prescription of nocturnal oxygen therapy (n = 74):* Nocturnal oxygen therapy was preceded by a course of continuous oxygen therapy in 34 patients (46%). Information on the initiation of nocturnal oxygen therapy was available in 61 patients (82%). According to the most accepted definition of “significant nocturnal oxygen desaturation”, the prescription of nocturnal oxygen therapy was inappropriate in 4 of the 61 patients (7%) for whom baseline nocturnal oximetry results were available.

**Conclusions:** Although the benefits of nocturnal oxygen therapy have yet to be confirmed, 20% of the patients with a primary diagnosis of COPD receiving oxygen therapy through our respiratory home care program were receiving home oxygen for nocturnal utilization only. Most prescriptions meet the current guidelines of home oxygen therapy. The most important area for further improvement is the systematic reevaluation of patients following the initial prescription of continuous oxygen therapy in the course of an acute exacerbation of the disease.

***Table 1. Nocturnal vs. continuous oxygen therapy in COPD at the Quebec City Respiratory Home Care Program***

	Nocturnal oxygen therapy	Continuous oxygen therapy	P
Number of patients	74	290	
Age, mean (SD)	74.3 (9.9)	74.6 (8.9)	0.8
Gender (male, n, %)	41.9%	44.8%	0.4
FEV1 % predicted, mean (SD)	47.4 (17.7)	37.6 (15.3)	< 0.0001
FEV1/FVC, mean (SD)	59.2 (17.6)	48.2 (15.3)	0.0001
Time (number of months) since the introduction of therapy (as of September 1, 2006), mean (SD)	22.8 (25.9)	31.5 (31.3)	0.02

ORIGINAL ARTICLE

## Nocturnal oxygen therapy in patients with chronic obstructive pulmonary disease: A survey of Canadian respirologists

Yves Lacasse MD MSc, Frédéric Sériès MD, Sylvie Martin MSc, François Maltais MD

Y Lacasse, F Sériès, S Martin, F Maltais. Nocturnal oxygen therapy in patient with chronic obstructive pulmonary disease: A survey of Canadian respirologists. *Can Respir J* 2007;14(6):343-348.

**BACKGROUND:** Current evidence does not clearly support the provision of nocturnal oxygen therapy in patients with chronic obstructive pulmonary disease (COPD) who desaturate during sleep but who would not otherwise qualify for long-term oxygen therapy (LTOT).

**OBJECTIVES:** To characterize the perception and clinical practice of Canadian respirologists regarding the indication and prescription of nocturnal oxygen therapy in COPD, and to determine what Canadian respirologists consider an important treatment effect of nocturnal oxygen therapy in a randomized, placebo-controlled trial.

**METHODS:** A mail survey of all the respirologists registered in the 2006 *Canadian Medical Directory* was conducted.

**RESULTS:** A total of 543 physicians were surveyed. The response rate was 60%, and 99% of the respondents indicated that the problem of nocturnal oxygen desaturation is clinically relevant. Eighty-two per cent interpret oximetry tracings themselves, and 87% have access to a sleep laboratory. Forty-two per cent believe that all COPD patients with significant nocturnal desaturation should have a polysomnography to rule out sleep apnea, and 41% would prescribe nocturnal oxygen therapy to asymptomatic patients. Assuming a risk of death or progression to LTOT of 40% over a three-year period, the respirologists indicated that to declare nocturnal oxygen therapy effective in reducing the risk of future clinical events in a clinical trial, the minimal absolute risk difference of death or progression to LTOT between oxygen and room air breathing should be 14%.

**CONCLUSIONS:** Canadian respirologists are interested in the issue of nocturnal oxygen desaturation in COPD. There is variation in clinical practices among Canadian respirologists, in several aspects of the management of this problem.

**Key Words:** COPD; Mail questionnaire; Oxygen therapy; Survey

Long-term oxygen therapy (LTOT) is the only component of the management of chronic obstructive pulmonary disease (COPD) that improves survival in patients with severe daytime hypoxemia (defined as an arterial oxygen pressure (PaO<sub>2</sub>) measured in the stable state of 55 mmHg or lower, or in the range of 56 mmHg to 59 mmHg when clinical evidence of pulmonary hypertension or polycythemia are noted) (1,2). Several studies (3-11) have demonstrated oxygen desaturation during sleep in patients with COPD. The earliest studies that described this phenomenon included patients with marked

### L'oxygénothérapie nocturne chez les personnes atteintes d'une maladie pulmonaire obstructive chronique : une enquête auprès des pneumologues canadiens

**HISTORIQUE :** Les données probantes courantes, n'étaient pas claires quant à l'administration d'oxygénothérapie nocturne chez les personnes atteintes d'une maladie pulmonaire chronique (MPOC) qui désaturent pendant leur sommeil mais qui ne seraient pas autrement éligibles à une oxygénothérapie à long terme (OTLT).

**OBJECTIFS :** Caractériser la perception et la pratique clinique des pneumologues canadiens au sujet des indications et de la prescription d'oxygénothérapie nocturne en cas de MPOC et déterminer ce que les pneumologues considèrent comme un effet important du traitement par oxygénothérapie nocturne dans le cadre d'un essai aléatoire contrôlé contre placebo.

**MÉTHODOLOGIE :** Les auteurs ont mené une enquête postale auprès de tous les pneumologues inscrits dans le *Canadian Medical Directory* de 2006.

**RÉSULTATS :** Au total, 543 médecins ont été sondés. Le taux de réponse était de 60 %, et 99 % des répondants ont indiqué que le problème de désaturation nocturne en oxygène était pertinent d'un point de vue clinique. Quarante-deux pour cent interprétaient eux-mêmes les tracés d'oxymétrie, et 87 % avaient accès à un laboratoire du sommeil. Quarante-deux pour cent étaient d'avis que toutes les personnes atteintes de MPOC devraient recevoir une importante désaturation nocturne devant recevoir une polysomnographie pour évaluer la possibilité d'apnée du sommeil. Quarante-un pour cent prescriraient une oxygénothérapie nocturne aux patients asymptomatiques. En supposant un risque de décès ou d'évolution vers l'OTLT de 40 % sur trois ans, les pneumologues ont indiqué qu'il faut déclarer l'oxygénothérapie nocturne efficace à réduire le taux d'événements cliniques majeurs dans le cadre d'un essai clinique, la différence minimale de risque absolu de décès ou d'évolution vers l'OTLT entre la respiration d'oxygène et l'air ambiant devrait s'élever à 14 %.

**CONCLUSIONS :** Les pneumologues canadiens s'intéressent à la question de l'oxygénothérapie nocturne en cas de MPOC. On remarque une variation de la pratique clinique des pneumologues en ce qui concerne divers aspects de la prise en charge de ce problème.

daytime hypoxemia qualifying for LTOT. Conventional LTOT, given 15 h/day to 18 h/day, compulsorily includes sleep time and therefore corrects sleep-related hypoxemia. However, sleep-related oxygen desaturation often occurs in patients not qualifying for LTOT. Sleep-related oxygen desaturation is considered by many physicians as an indication for providing nocturnal oxygen therapy in patients who would not otherwise qualify for LTOT. This perceived indication stems from the suggestion that the natural progression of COPD to its end stages of chronic pulmonary hypertension, severe hypoxemia,

Centre de recherche, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie de l'Université Laval, Sainte-Foy, Québec  
Correspondence: Dr Yves Lacasse, Centre de pneumologie, Hôpital Laval, 2725 Chemin Sainte-Foy, Sainte-Foy, Québec G1V 4G5.  
Telephone 418-656-4747, fax 418-656-4762, e-mail yves.lacasse@med.ulaval.ca

lacasse et al

right heart failure and death is dependent on the severity of desaturation occurring during sleep (12,13).

Despite the lack of clear guidance by scientific societies regarding the indications for and use of nocturnal oxygen therapy in COPD patients not qualifying for conventional LTOT, a number of patients are currently treated with nocturnal oxygen (14). This is occurring even after two small randomized, controlled trials (15,16) and their meta-analysis (17) do not clearly support this clinical practice. Further research is warranted in this area.

We report the results of a mail survey of Canadian respirologists that was conducted with the primary objective of characterizing their perception and clinical practice regarding the indications and prescription of nocturnal oxygen therapy in patients with COPD. Our secondary objective was to determine what Canadian respirologists consider as an important treatment effect of nocturnal oxygen therapy in a placebo (room air) controlled clinical trial. The present study is an important preliminary step in our planning of a national multicentre, randomized, controlled trial of oxygen therapy in patients with COPD, in which the primary outcome is a composite of all-cause mortality or progression to LTOT.

## METHODS

### Study population

A total of 543 respirologists who were registered in the 2006 Canadian Medical Directory, which lists more than 90% of the physicians currently licensed in the country, were surveyed.

### Questionnaire

The mail survey was organized into four sections. The first section was designed to collect general information about the respondents, including sex, year of graduation, clinical experience with the management of COPD, and their involvement in the organization and/or delivery of home oxygen therapy services in their area. The second section related to the diagnosis and treatment of nocturnal desaturation. In this section, the questionnaire included four short scenarios to examine the perceived indications for nocturnal home oximetry in specific clinical circumstances.

The third section of the questionnaire was to determine what Canadian respirologists consider as a minimal important treatment effect of nocturnal oxygen therapy on mortality or disease progression. Such information has important implications for sample-size calculation in randomized trials (18). The following background information was provided:

Although nocturnal oxygen is often prescribed in patients with COPD, the magnitude of its treatment effect (if any) remains unknown. From the current literature, we know that, over a three-year period: the mortality of patients with moderate-to-severe COPD not qualifying for LTOT but who desaturate overnight is about 20%; and an additional 20% will be prescribed LTOT because of disease progression. Therefore, the three-year major clinical event rate (including progression to severe hypoxaemia necessitating LTOT or death) in this group of patients is roughly 40%.

The supporting references (16,19) were not cited in the questionnaire. The minimal important difference was determined using two different questions. The first one addressed the issue of benefit of nocturnal oxygen in terms of absolute risk reduction: "To what proportion would you like to see nocturnal oxygen therapy decrease this event rate before declaring

it to be clinically effective". The second question directly elicited a number needed to treat (NNT) ("To consider nocturnal oxygen therapy effective in patients with COPD, to how many patients would you be willing to administer nocturnal oxygen to prevent one patient from a major clinical event [ie, death or progression to LTOT] over a 3-year period").

In the final section of the questionnaire, the respondents were invited to inform the authors about their potential interest in participating in a future randomized trial of nocturnal oxygen therapy in COPD patients. The French version of the questionnaire was pilot-tested on five respirologists and translated into English after modifications and clarifications were made. Five minutes were sufficient to complete the questionnaire.

### Survey

The survey was conducted in April and May 2006 according to the 'total design method' described by Dillman (20). Each respirologist was mailed a package containing a cover letter, a questionnaire in his/her language (French or English) and a prepaid reply envelope. Each questionnaire was numbered and coded for identification, and to protect confidentiality. This first shipping was then followed after one week by a reminder postcard. Four weeks later, those who had not responded to the initial questionnaire were sent a second package that was identical to the first one, except for the cover letter mentioning that their questionnaire had not yet been received.

### Statistics

**Response rate:** The response rate was calculated as the ratio of analyzable responses over the number of eligible physicians that were reached (21):

$$\text{Response rate} = \frac{\text{Number of respondents contributing to the analysis}}{\text{Number of questionnaires sent} - (\text{Noneligible} + \text{Nonreachable})}$$

Physicians who returned their questionnaire indicating that they do not see patients presenting with COPD in their practice were designated 'noneligible'. Physicians whose first package was returned to us were designated 'nonreachable'. Newfoundland and Labrador, Nova Scotia, Prince Edward Island and New Brunswick were analyzed as the 'Atlantic provinces', and Alberta, Saskatchewan and Manitoba as the 'Prairies'. The other provinces (Ontario, Quebec and British Columbia) were analyzed separately. A response rate of 60% was predicted a priori (21).

**Analysis:** Descriptive statistics (proportions and means  $\pm$  SDs when appropriate) were used to characterize the respondents and to report the results of the survey. For each respondent, the absolute risk difference corresponding to the minimal important difference in major event rate between treated patients and untreated patients was calculated by subtracting the expected event rate in the treated group (elicited by the questionnaire) from the estimated event rate in the untreated group (which was assumed to be 40%). From this absolute risk difference, the corresponding NNT was computed (computed NNT/absolute risk difference). Finally, the concordance between the computed NNT and the elicited NNT using the intraclass correlation coefficient was examined (22).

## RESULTS

### Respondents

Five hundred forty-three respirologists were sent the questionnaire, and 332 replied. Of these respondents, 280 completed



# Nocturnal oxygen in COPD

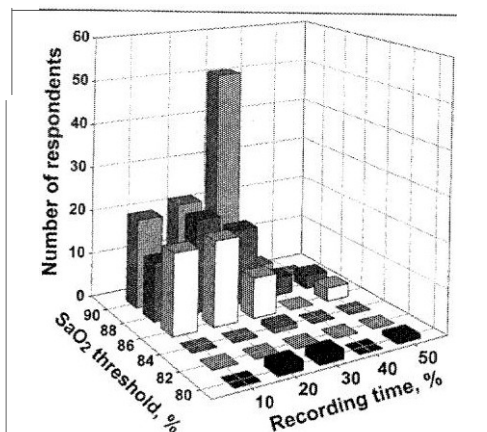


Figure 1) Definition of 'significant nocturnal oxygen desaturation' (115 respondents; four outliers do not appear on the graph) expressed in terms of percentage of the recording time spent below a given threshold saturation. SaO<sub>2</sub> Arterial oxygen saturation

the questionnaire and 52 indicated that they are not involved in the care of patients with COPD. Twenty-three packages were returned by the post office as undeliverable. Therefore, the response rate among potentially eligible respondents was (332-52)/(543-[52+23]), or 60%.

All the regions of the country were represented, with response rates ranging from 80% in the Atlantic provinces to 49% in the Prairies. Twenty-three per cent of the respondents were female. On average, the respondents were in clinical practice for 23±9 years. A significant proportion of the respondents' clinical practice was dedicated to the care of patients with COPD (mean 30±17%). One hundred fifty-three (54%) indicated that they are involved in the organization and/or delivery of home oxygen therapy in their area.

## Diagnosis and treatment of nocturnal desaturation

Only four respondents (1%) indicated that the problem of nocturnal oxygen desaturation in patients with COPD should not be considered. These respondents were instructed not to go further in the questionnaire and to return it as is.

Among the other 276 respondents, 87% indicated that they have already prescribed nocturnal oxygen; 97% have access to pulse oximeters, and 82% interpret oximetry tracings themselves. In addition, 87% of the respondents have access to a sleep laboratory in their institution. For 42% of the respondents, a full sleep study was deemed necessary in all cases to rule out sleep apnea. Fifty-seven per cent of the respondents indicated that one abnormal recording is sufficient to prescribe nocturnal oxygen; two abnormal recordings are necessary for 35%, and the respondents. Forty-one percent of the respondents would prescribe home oxygen (either LTOT or nocturnal oxygen only) to active smokers.

The question related to the definition of 'significant nocturnal oxygen desaturation' generated a wide range of responses. The vast majority (95%) indicated that the time spent below a given threshold is an important factor defining nocturnal oxygen desaturation. However, both the time and

TABLE 1  
Perceived indications of nocturnal home oximetry in specific clinical circumstances (n=276)

Clinical scenario	Number (%) of respondents who would request a nocturnal oximetry
<b>Scenario #1</b>	
Mr W is a 63-year-old patient with severe chronic obstructive pulmonary disease (COPD). He has been stable during the previous year. His resting oxygen saturation is 93%.	48 (17.4)
<b>Scenario #2</b>	
Ms X is a patient with physical signs of right heart failure who otherwise does not qualify for long-term oxygen therapy	269 (97.5)
<b>Scenario #3</b>	
Mrs Y was hospitalized two months ago for an acute exacerbation of COPD that was complicated by severe hypoxemia. She then left the hospital with a new prescription of home oxygen. Upon re-evaluation, her resting PaO <sub>2</sub> (at room air) is now 65 mmHg.	138 (50.0)
<b>Scenario #4</b>	
Mr Z is a 74-year-old patient with severe COPD (FEV <sub>1</sub> 36% predicted) who snores and complains of mild daytime sleepiness.	269 (97.5)

FEV<sub>1</sub> Forced expiratory volume in 1 s; PaO<sub>2</sub> Arterial oxygen pressure

the threshold varied considerably among respondents (Figure 1). Approximately one-third of the respondents (34%) also considered the average saturation over the entire recording time to be important. The average saturation (88±2%) was quite similar among respondents (n=90). Finally, the lowest saturation (79±5%) reached during the night was also important for 25% of the respondents (n=62). Sixty-three respondents identified other factors defining 'significant nocturnal desaturation', the most frequent being polycythemia, cor pulmonale, symptoms of left heart failure at night, ventricular cardiac arrhythmias and unstable ischemic heart disease.

The clinical scenarios and the associated responses are presented in table 1. Clearly, the respondents would not screen for nocturnal oxygen desaturation in patients with stable COPD (scenario #1). Physical signs of right heart failure without severe daytime hypoxemia would prompt most respondents to look for nocturnal oxygen desaturation (scenario #2). The finding of an adequate PaO<sub>2</sub> at the time of re-evaluation, following an acute exacerbation complicated by severe hypoxemia, was seen as an indication of looking for nocturnal desaturation in one-half of the respondents (scenario #3). Finally, the vast majority of respondents would look for sleep apnea even in elderly patients with severe COPD (scenario #4).

Determination of the minimal clinically important difference. The absolute risk difference considered as minimal to declare nocturnal oxygen therapy effective in reducing the rate of major clinical events compared with room air breathing was 14±6%. The mean computed NNT was 9. When directly elicited by the questionnaire, the mean NNT was 13±12. No concordance was found between the computed NNT and the NNT directly elicited by the questionnaire (intraclass correlation coefficient of 0.0; Figure 2).

Lacasse et al

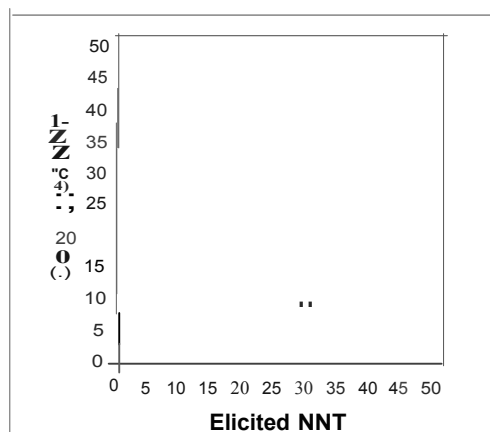


Figure 2) Unk of concordance betw> the Computed number needed to treat (NNT) and the elicited NNT

#### Interest in participating in a future randomized trial

One hundred eight respondents (39%) from all regions of Canada indicated that they would be interested in participating in a randomized trial of nocturnal oxygen therapy in patients with COPD.

#### DISCUSSION

The response rate we obtained (60%) was typical of physicians' reply to mailed survey, which usually averages 50% to 55% (21). We attempted to investigate the potential for non-response bias by making a priori predictions on the response rate, and by examining the representation in the survey of physician from all the regions in the country. The overall response rate met our a priori prediction. Also, all parts of Canada were represented in the survey.

Why should respirologists be interested in nocturnal oxygen desaturation? COPD clearly represents a significant burden of health care systems wherever it has been assessed (23). Home oxygen therapy comes in second place (only after hospitalizations) among the most expensive health care resources for COPD (24). In the Canadian cohort of the Confronting COPD survey (24) (3265 individuals; mean age of 63 years; 44% female), outpatient treatment for COPD accounted for over 30% of total direct costs, the majority of which was for home oxygen therapy. Overall, home oxygen therapy accounted for almost 20% of the entire annual direct costs for COPD (24). Informal surveys among respiratory home care programs in Quebec indicate that 15% to 20% of those who receive home oxygen therapy through these programs have been prescribed oxygen for nocturnal use only. Given the resources allocated to nocturnal oxygen therapy, its prescription should therefore be justifiable by demonstrating an improvement in clinical outcomes other than the mere correction of nocturnal oxygen desaturation.

However, the current evidence that nocturnal oxygen therapy prolongs survival comes only from the indirect comparison of the results of the British Medical Research Council Study (1) with those of the Nocturnal Oxygen Therapy Trial of the

TABLE 2

Key elements of the upcoming Canadian Nocturnal Oxygen (CANOX) trial

#### Study population

Patients with chronic obstructive pulmonary disease fulfilling the definition of nocturnal oxygen desaturation, ie, 30% or more of the recording time with transcutaneous arterial oxygen saturation lower than 90% on two consecutive recordings. Patients with sleep apnea were excluded.

#### Intervention

Nocturnal oxygen therapy delivered overnight to allow the oxygen saturation to be higher than 90%; placebo (room air) delivered by a defective concentrator (sham concentrator).

#### Outcome

Composite of either all-cause mortality or requirement for long-term oxygen therapy.

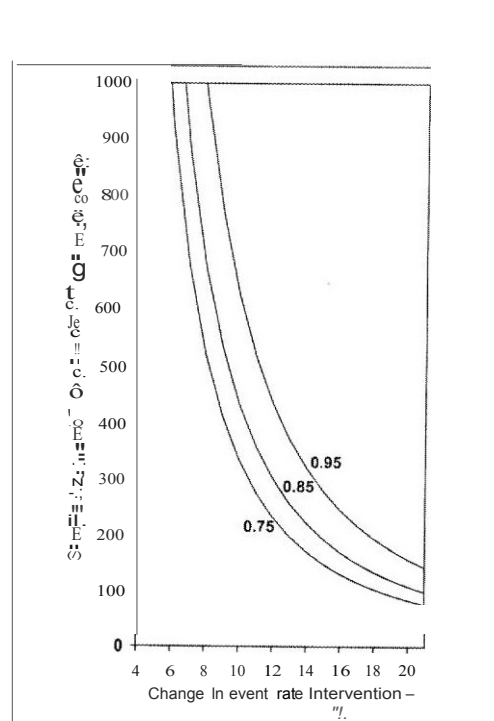
#### Design

Three-year multicentre, placebo-controlled, randomized trial.

National Heart, Lung, and Blood Institute (2), and these results apply only to severely hypoxemic patients with COPD, ie, those with a diurnal  $PaO_2$  of 55 mmHg or lower. To date, only two randomized trials directly addressed the issue of nocturnal oxygen therapy in patients with COPD with significant nocturnal oxygen desaturation who would not otherwise qualify for LTOT (15,16). The recent meta-analysis by Cranston et al (17) concluded that nocturnal oxygen has no effect on survival (pooled OR 0.97; 95% CI 0.41 to 2.31). However, the authors did not comment on the lack of precision in the effect estimate.

Among the recent COPD treatment guidelines (25-28), only the Canadian document (28) addressed the issue of nocturnal oxygen therapy, albeit in vague terms. Two recent workshops of the National Heart, Lung, and Blood Institute identified nocturnal oxygen therapy as a research priority in COPD (25,29). This situation stimulated our planning of a randomized trial of nocturnal oxygen therapy in patients with COPD, the Canadian Nocturnal Oxygen (CANOX) trial, in which the ultimate objective would be to examine the effect of nocturnal oxygen on mortality and disease progression requiring LTOT (Table 2).

The design of a randomized controlled trial of nocturnal oxygen raises important methodological problems in the choice of the primary outcome. In such a trial, wherever the treatment received, the condition of participants may deteriorate to the point that LTOT is required. This situation is particularly problematic because LTOT compulsorily includes sleep time (and therefore nocturnal oxygen therapy). LTOT would thus represent an important contaminant and a threat to the validity of the trial. Therefore, a composite of mortality or progression to LTOT would constitute the primary outcome of the trial. The choice of a composite outcome requires that its components are of similar importance, occur with similar frequency and have similar RR reduction (30). Whether disease progression requiring LTOT has the same weight as death for patients with severe COPD is debatable. However, we know that the prescription of LTOT is a marker of disease progression and a strong predictor of mortality (31-33). It is also associated with poor functional status, impaired quality of life and depression (34). Of note, in a trial by Chaouar et al (16), mortality and progression to LTOT were well balanced in proportion, and moved in the same direction.



control groups,

Figure 3) Sample sizes (number of patients per group) required to detect absolute risk differences between treated and untreated patients, each two-sided significance level of 0.05 and varying study powers (0.75, 0.85 and 0.95). The risk of a major clinical event in the untreated group is assumed to be 40%.

The results of our survey provided useful information for the planning of the CANOX trial. We were particularly interested in determining what Canadian respirologists consider as the minimal important difference in major event rate (ie, mortality or progression to LTOT) between untreated patients (room air) and treated patients (nocturnal oxygen). Our finding of a poor concordance between the computed NNT and that directly elicited by the questionnaire was of no surprise. Previous studies (21,35,36) also suggested that physicians' enthusiasm for therapy varies when the data are presented with the NNT compared with the absolute risk reduction. Assuming a major event rate of 40% in the untreated group, we determined that 221 patients per group were needed to demonstrate a 14% difference in event rates between the two study groups (power 85%; alpha error 5%, two-sided) (37). If the sample size was increased to 300 patients per group, the difference to be detected is 12%. Figure 3 illustrates that small change in the difference to be detected have a huge impact on the needed sample size.

We clarified other components of the CANOX trial's protocol from the results of the present survey. The first one relates to the diagnosis of sleep apnea in patients with severe COPD and the routine use of polysomnography in such patients. Approximately 60% of the respondents would accept to confidently diagnose nocturnal oxygen desaturation alone

#### Nocturnal oxygen in COPD

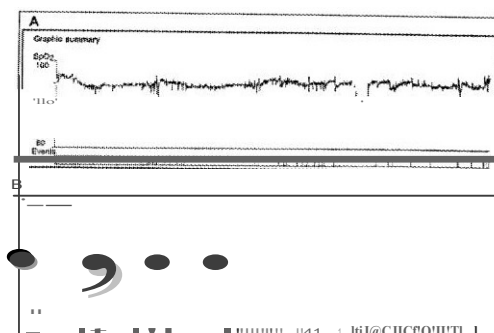


Figure 4) Nocturnal oximetry tracings in patients with chronic obstructive pulmonary disease not qualifying for long-term oxygen therapy. A Nocturnal oxygen desaturation (30% or more of the recording time with an oxygen saturation lower than 90%) with nonperiodical variation in saturation throughout sleep. This tracing is non suggestive of sleep apnea. B Next-normal oxygen desaturation with cyclical changes in saturation suggesting sleep apnea. SpO<sub>2</sub> Arterial oxygen saturation

on the basis of oximetry tracings only. Given the limited access to diagnostic facilities for patients with suspected sleep apnea in Canada (38), this argues in favour of a pragmatic approach for the inclusion of patients in the study on the basis of the pretest probability of sleep apnea and the results of oximetry tracings (Figure 4). The second issue relates to the inclusion of active smokers in the trial. Forty-one per cent of the respondents would prescribe nocturnal oxygen therapy to active smokers. Although less than desirable (39), this situation is a reflection of current practices in Canada that are not about to change. The current version of the study protocol does not exclude current smokers from the trial. A stratified randomization process should be used to ensure that smokers are equally distributed in treated and untreated patients.

Finally, that 105 respirologists expressed their willingness to participate in a multicentre trial of nocturnal oxygen therapy is very supportive and clearly demonstrates the interest raised by the problem of nocturnal oxygen desaturation in COPD patients. Our finding of variations in clinical practices in several aspects of the management of nocturnal oxygen desaturation is also an indication that further research is warranted. The present survey provided important information for the planning of a national randomized, placebo-controlled trial of nocturnal oxygen therapy in COPD.

ACKNOWLEDGEMENT: We thank the respirologists who took the time to reply to our survey.

#### REFERENCES

1. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1981; i:681-6.
2. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Nocturnal Oxygen Therapy Trial Group. N Engl J Med 1980; 303:354-8.
3. Leitch AG, Clancy LJ, Legg JR, Tweed JC, Tait J, Watson P, Evans JI. Arterial blood gas tensions, hydrogen ion, and cerebroencephalic flow during sleep in patients with chronic ventilatory failure. Thorax 1976; 31:730-5.

## APPENDIX 3

### PREVALENCE AND DETERMINANTS OF NOCTURNAL OXYGEN DESATURATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Yves Lacasse<sup>1</sup> MD, MSc, Nada Vujovic-Zotovic<sup>2</sup> MD, Roger Goldstein<sup>2</sup> MB ChB, Jean Bourbeau<sup>3</sup> MD, MSc, Frédéric Sériès<sup>1</sup> MD, Richard Lecours<sup>4</sup> MD, Shawn Aaron<sup>5</sup> MD, MSc, François Maltais<sup>1</sup> MD

<sup>1</sup>Centre de recherche, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie de l'Université Laval, Québec; <sup>2</sup>West Park Hospital, Department of Medicine and Physical Therapy, University of Toronto; <sup>3</sup>Montreal Thoracic Institute, McGill University, Montreal; <sup>4</sup>Service de pneumologie, Centre hospitalier affilié de l'Hôtel-Dieu de Lévis, Lévis; <sup>5</sup>Ottawa Health Research Institute, University of Ottawa.

**Background:** The proportion of patients with moderate/severe COPD not qualifying for long-term oxygen therapy (LTOT) who present nocturnal oxygen desaturations is not well characterized. This statistic is of outmost importance in our planning of a randomized trial of nocturnal oxygen therapy in COPD (the International Nocturnal Oxygen – INOX - trial). The feasibility of this trial as well as the resources allocation depend on the proportion of patients with moderate/severe COPD not qualifying for LTOT who present nocturnal oxygen desaturation.

**Objectives:** To determine, in patients with moderate-to-severe COPD not qualifying for long-term oxygen therapy (LTOT), the proportion of nocturnal desaturators.

**Desing:** Cross-sectional study.

**Setting:** 5 clinical sites that are planning the INOX trial.

**Patients:** The inclusion (and exclusion) criteria for this pilot study were the same as those that will apply in the INOX trial. Briefly, we included patients: (1) with a diagnosis of COPD supported by an history of past or current smoking and obstructive disease with an FEV1 < 50% predicted, an FEV1/FVC < 60% and a total lung capacity > 80% predicted; (2) with mild-to-moderate daytime hypoxemia with a daytime paO<sub>2</sub> in the range of 56-69 mmHg; and (3) stable COPD at the time of the study, as demonstrated by no acute exacerbation and no change in the medication for at least 6 weeks before the enrollment in the study. Preliminary data obtained from a small convenience sample of patients (n = 12) indicated that about 25% of the patients with moderate-to-severe COPD meeting these criteria are nocturnal desaturators (unpublished data). We determined that a sample size of 128 patients is needed for the precision of the proportion of desaturators to be no more than  $\pm 7.5\%$

**Measurements:** Within 1 month of the first nocturnal oximetry, we obtained baseline clinical characteristics, pulmonary function tests (including spirometry, lung volumes and carbon monoxide diffusion capacity). We measured arterial blood gases while patients were breathing at room air. Nocturnal saturation (SaO<sub>2</sub>) monitoring was obtained with a continuous digital recording system (Nonin Medical Inc., Plymouth, MN, USA). For each patient, two oximetries were obtained over a 2-week period. Patients were classified in 3 categories according to the same criteria that will apply in the INOX trial: (a) no nocturnal desaturation (i.e., < 30% of the recording time with an oxygen saturation < 90% on both oximetries); (b) nocturnal desaturation (i.e.,  $\geq 30\%$  of the recording time with an oxygen saturation < 90%) with suspicion of associated sleep apnea (i.e., cyclical changes in saturation in addition to the desaturations on either of the oximetries); (c) nocturnal desaturation (i.e.,  $\geq 30\%$  of the recording time with an oxygen saturation < 90%) without suspicion of associated sleep apnea (i.e., steady tracing with non-periodic variation in saturation throughout sleep on both oximetries).

**Results:** 128 patients (62% male; mean age: 70; SD: 8); mean FEV1%predicted: 37%; SD: 11) contributed to the analysis. The recording time with an oxygen saturation < 90% in both oximetries

was highly correlated ( $r = 0.84$ ;  $p < 0.0001$ ), indicating consistency in desaturation captured on consecutive oximetry recordings. Fifty-one of the 128 patients were classified as nocturnal desaturators without suspicion of sleep apnea (40%; 95% confidence interval: 31 – 49). These patients represent those eligible in the INOX trial. In addition, 16 patients (13%) were classified as desaturators with suspicion of sleep apnea. In the INOX trial, these patients may be submitted to polysomnography in order to rule out sleep apnea. Baseline characteristics and results of physiological measures are compared in Table 1 and 2 respectively. We found no significant difference in baseline characteristics or physiological measures among the 3 groups that could predict nocturnal desaturation without suspicion of sleep apnea, with the exception of body mass index. The most significant predictor of nocturnal oxygen desaturation was baseline saturation measured at the opening of the oximeter (Table 3).

**Conclusions:** A significant proportion (40%) of patients with moderate-to-severe COPD not qualifying for LTOT has nocturnal oxygen desaturation without evidence of sleep apnea. This phenomenon cannot be reliably predicted by any simple anthropometric or physiological measure.

***Table 1: Baseline characteristics (n = 128)***

	Nocturnal desaturation without suspicion of sleep apnea (n = 51)	Nocturnal desaturation with suspicion of sleep apnea (n = 16)	No nocturnal desaturation (n = 61)	P value
Age	68.4 (7.7)	68.0 (8.6)	71.0 (7.8)	0.09
Gender (% male)	52.9	75.0	65.6	0.2
BMI	24.9 (4.8)	30.8 (6.4)	24.3 (5.0)	0.0007
Current smokers (%)	17.6	18.8	14.8	0.9
Pack-years	49.5 (24.5)	61.8 (30.3)	48.9 (23.9)	0.2
Theophylline	9.8%	12.5%	23.0%	0.2
Tiotropium	82.4%	68.8%	83.6%	0.4
LABA	92.2%	87.5%	83.6%	0.4
Inhaled steroids (ICS)	62.7%	62.5%	65.6%	0.9
Combinations (LABA + ICS)	45.1%	50.0%	50.8%	0.8
Prednisone	5.9%	6.3%	4.9%	1.0

**Table 2 : Arterial blood gases and pulmonary function tests results (n = 128)**

	Nocturnal desaturation without suspicion of sleep apnea (n = 51)	Nocturnal desaturation with suspicion of sleep apnea (n = 16)	No nocturnal desaturation (n = 61)	P value
pH	7.4 (0.4)	7.4 (0.03)	7.4 (0.02)	0.12
pCO <sub>2</sub>	42.6 (4.9)	45.2 (5.9)	42.1 (4.3)	0.20
pO <sub>2</sub>	63.7 (4.1)	65.2 (3.4)	65.8 (2.9)	0.03
Hb	144.5 (14.6)	142.3 (9.5)	146.1 (13.8)	0.6
FEV <sub>1</sub> %	35.3 (11.7)	35.3 (11.8)	35.5 (10.0)	0.7
FVC %	80.0 (16.9)	69.4 (21.6)	78.8 (22.4)	0.08
FEV <sub>1</sub> / FVC	34.3 (10.6)	42.5 (13.7)	35.2 (9.5)	0.05
FRC %	166.1 (31.3)	151.3 (33.2)	165.9 (35.7)	0.4
TLC %	127.0 (18.3)	116.4 (19.3)	127.5 (22.9)	0.2
RV %	193.3 (43.9)	182.2 (52.6)	192.9 (56.8)	0.7
DLCO %	41.1 (13.2)	56.4 (20.0)	45.5 (16.7)	0.03

**Table 3: Nocturnal oximetry results<sup>1]</sup> (n = 128)**

	Nocturnal desaturation without suspicion of sleep apnea (n = 51)	Nocturnal desaturation with suspicion of sleep apnea (n = 16)	No nocturnal desaturation (n = 61)	P value
Recording time (hours)	7.5 (1.4)	7.3 (1.1)	7.4 (1.4)	0.8
Desaturation index	5.4 (4.1)	23.8 (16.0)	5.5 (5.9)	< 0.0001
Baseline saturation	88.6 (2.3)	89.0 (3.6)	92.0 (1.2)	< 0.0001
Average saturation	85.8 (2.7)	84.8 (3.3)	89.0 (1.9)	< 0.0001
% recording time with saturation 90%	60.6 (25.7)	62.8 (24.6)	10.4 (12.8)	< 0.0001

<sup>1</sup> Only the results of the second oximetry are shown.

## APPENDIX 4

### NOCTURNAL OXIMETRY ALONE OR POLYSOMNOGRAPHY TO RULE OUT SLEEP APNEA IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE? A VALIDATION STUDY

Yves Lacasse MD, SMc, François Maltais MD, Frédéric Sériès MD. *Centre de recherche, Centre de Pneumologie, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie de l'Université Laval, Québec, Canada.*

**Background :** Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are common conditions. The combination of COPD and OSA is referred to as the “overlap syndrome”. We recently demonstrated that 40% of patients with COPD and moderate hypoxemia (daytime  $\text{paO}_2$  in the range of 56-69 mmHg) exhibit nocturnal oxygen desaturation. Two different patterns of nocturnal oxygen desaturation are seen on oximetry tracings: (1) steady nocturnal desaturation with non-periodic variation in saturation throughout sleep; and (2) nocturnal desaturation with cyclical changes in saturation. Typical tracings are shown in Appendix 11. Whether the diagnosis or the exclusion of obstructive sleep apnea must rely on a laboratory or ambulatory polysomnography is uncertain.

**Objectives :** To determine the accuracy of home nocturnal oximetry to distinguish between OSA and nocturnal oxygen desaturation alone in patients with moderate-to-severe COPD who exhibit significant nocturnal oxygen desaturation.

**Methods:** This study involved, in a blind comparison of home nocturnal oximetry and laboratory polysomnography in patients with nocturnal oxygen desaturation. Patients: We conducted in 2006 a multi-centre cross-sectional study with the objective to determine, in an unselected population of patients with COPD and moderate daytime hypoxemia, the proportion of nocturnal oxygen desaturators and the predictors of this phenomenon. Five clinical centres in Quebec and Ontario participated in this study that enrolled 128 patients. Forty-nine (49) patients from Laval Hospital contributed to this analysis. Among these 49 patients, 23 had significant nocturnal oxygen desaturation diagnosed by home oximetry alone. Home oximetry: For the purpose of the cross-sectional study, we obtained continuous nocturnal saturation ( $\text{SaO}_2$ ) monitoring with a digital recording system (Nonin Medical Inc., Plymouth, MN, USA). Recordings of at least 4 hours were mandatory. For each patient, two oximetries were obtained over a maximal period of 2 weeks. We defined “nocturnal desaturation” as  $\geq 30\%$  of the recording time (time in bed) with a transcutaneous arterial oxygen saturation  $< 90\%$ . Each patient was then classified in one of 2 categories on the basis of 2 consecutive recordings, according to the recording time with an oxygen saturation  $< 90\%$  along with the visual inspection of the printed report: (1) nocturnal desaturation without suspicion of associated sleep apnea (i.e., steady  $\text{SaO}_2$  tracing with non-periodic variation in saturation throughout sleep on either of the oximetries); and (2) nocturnal desaturation with suspicion of associated sleep apnea (i.e., cyclical changes in saturation in addition to the stable desaturations on either of the oximetries). All reports were reviewed by a sleep specialist (FS) with extensive experience and special interest in oximetry assessment for final patient classification. We recalled these 23 patients to obtain an in-lab polysomnography to validate our classification by home nocturnal oximetry alone. For the purpose of this validation study, we obtained an additional oximetry with the same system in order to ascertain the desaturation pattern of these patients. Gold standard: polysomnography: Within 2 weeks of the home nocturnal oximetry, each patient underwent a polysomnographic study. The polysomnographic recordings consisted in continuous acquisition of electroencephalogram, electrooculogram, submental electromyogram, naso-oral airflow with thermistors, nasal pressure with nasal cannula, chest and abdominal movements with impedance plethysmography (RespirtraceÆ, Ambulatory Monitoring Inc, Ardsley, NY), electrocardiogram, and breath sounds by means of two microphones connected to a calibrated sound

analyzer. Sleep position was continuously assessed by the attending technician on the monitor of an infrared camera. All variables were digitally recorded (Sandman Elite™ system, Mallinckrodt, Kenilworth, NJ). Sleep and respiratory variables were scored according to standard criteria. Sleep apnea was considered to be significant when the apnea/hypopnea index  $\geq 15/h$ .

**Results:** From the 23 patients identified as nocturnal desaturators in cross-sectional study, 18 were available for this study; 11 underwent an in-lab sleep study (Figure 1, next page). Details of the results are provided in Table 1. Upon reevaluation in the validation study, one patient (No. 9) had normal oximetry whereas she previously desaturated in the cross-sectional study. Her sleep recording was normal. This patient was excluded from further analysis. In the 10 other patients, the results of the home oximetry recordings were concordant with those of the cross-sectional study. OSA was ruled out in the 5 patients who were classified as “nocturnal desaturators without suspicion of associated OSA”. In the 5 patients who were classified as “nocturnal desaturators with suspicion of OSA” on oximetry recordings, OSA was confirmed in 3 (Table 2).

**Table 1. Patients’ classification according to nocturnal oximetry and polysomnography**

Patient no.	Classification in the cross-sectional study by oximetry alone	Validation study	
		Classification by oximetry	Result of polysomnography
1	No OSA suspected	No OSA suspected	OSA -
2	No OSA suspected	No OSA suspected	OSA -
3	No OSA suspected	No OSA suspected	OSA -
4	No OSA suspected	OSA suspected	OSA -
5	No OSA suspected	No OSA suspected	OSA -
6	OSA suspected	OSA suspected	OSA +
7	OSA suspected	OSA suspected	OSA +
8	OSA suspected	OSA suspected	OSA +
9	No OSA suspected	No significant desaturation	OSA -
10	No OSA suspected	No OSA suspected	OSA -
11	OSA suspected	OSA suspected	OSA -

**Table 2. Accuracy of home nocturnal oximetry to detect sleep apnea in COPD**

		Polysomnography (gold standard)		Total
		OSA	No OSA	
<b>Home nocturnal Oximetry</b>	OSA suspected	3	2	5
	No OSA suspected	0	5	5
<b>Total</b>		3	7	10

**Conclusion :** In patients with significant nocturnal oxygen desaturation, home nocturnal oximetry has high negative predictive value for the diagnosis of OSA : OSA may be ruled out in patients with oximetry tracings demonstrating significant nocturnal desaturation with non-periodic variation in saturation throughout sleep. However, home nocturnal oximetry has a poor positive predictive value for the diagnosis of OSA.



**Figure 1.**

---

23 Patients with significant nocturnal oxygen desaturation in the cross-sectional study

---

- |                           |
|---------------------------|
| 1 moved away              |
| 2 were prescribed CONT-O2 |
| 2 died                    |

---

18 Patients available for the validation study

---

- |  |
|--|
| 4 refusals                               |
| 3 exacerbations at the time of the study |

---

11 Patients in the validation study

---

## APPENDIX 5

### UTILITY SCORES IN PATIENTS WITH OXYGEN-DEPENDENT COPD

Yves Lacasse MD, MSc, Sylvie Martin MSc, François Maltais MD. *Centre de recherche, Centre de Pneumologie, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie de l'Université Laval, Québec, Canada.*

**Background :** The comparison of health-related quality of life among patients with different chronic health condition is essential to the prioritization of limited health resources from cost-effectiveness analyses. To do so, utility measures use a preference-based or value-based approach to express the health-related quality of life of an individual using a single number. This number incorporates the overall assessment of health-related quality of life and the values attached to it. This number is usually between 0 and 1. The two extreme values are anchored to specific states, most commonly death (0) and full health (1). The utility of patients with oxygen-dependent chronic obstructive pulmonary disease (COPD) is unknown.

**Objectives:** To determine the utility of patients with oxygen-dependent COPD.

**Design:** Cross-sectional study.

**Patients:** We surveyed patients with oxygen-dependent COPD registered at the Quebec City area Respiratory home care program. This program is funded by the Quebec universal medical insurance plan and delivers home care (mainly home oxygen therapy and related services) to registered patients with any chronic lung disease. Oxygen dependence was defined as severe hypoxemia ( $\text{PaO}_2 \leq 55$  mmHg; OR  $\text{PaO}_2 \leq 59$  mmHg with clinical evidence of at least one of the following: (1) pulmonary hypertension; (2) right ventricular hypertrophy; (3) cor pulmonale; (4) hematocrit  $\geq 55\%$ <sup>1</sup>) requiring continuous oxygen therapy (CONT-O2, i.e.,  $\geq 18$  hours per day).

**Measures:** We used the SF-6D<sup>2</sup>, a preference-based single index derived from the SF-36.

**Results:** 105 patients were surveyed; 3 did not provide complete SF-36 data. The clinical characteristics of the 102 patients who did complete the SF-36 are summarized in Table 1. The mean utility score was 0.60 (SD: 0.11). Women (n = 43) and men (n = 59) had similar utility scores (0.59 vs. 0.61 respectively, p = 0.37). For comparison, utility scores associated with several health conditions are provided in Table 2 (below).

<sup>1</sup> Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980; 93: 391-398.

<sup>2</sup> Brazier J, Usherwood T, Harper R, et al. Deriving a preference-based single index from the UK SF-36 Health Survey. *J Clin Epidemiol* 1998; 51: 1115-28.

*Table 1. Clinical characteristics of patients<sup>a</sup>*

<b>Characteristics</b>	<b>(n = 102)</b>
Gender	59 males : 43 females
Age (years)	71 (65 - 77)
Mean FEV <sub>1</sub> (% pred.)	34% (25 - 44)
Past medical history (number of major medical diagnoses, excluding COPD <sup>b</sup> )	0 (0 - 1)
Time since the introduction of continuous oxygen therapy (months)	19 (9 – 32)
Number of drug prescriptions	7 (6 - 10)
Leaving with spouse	73%

<sup>a</sup> For clarity and uniformity, results are presented (unless otherwise specified) as medians (interquartile range);

<sup>b</sup> Six diagnostic categories were considered: heart failure, ischaemic heart disease, diabetes, stroke, musculoskeletal disease, and cancer.

**Interpretation:** Health-related quality of life of patients with oxygen-depend COPD is severely impaired. The prescription of CONT-O2 is a critical step in the life of patients with severe COPD.

**Discussion: implication for the construction of the INOX trial's composite outcome - an example from the cardiovascular literature:** A composite outcome is an event that is considered to have occurred if one of several different events or outcomes is observed<sup>3</sup>. Although a composite outcome may increase the event rate (and thus the statistical power) of the study, it may mislead if its components are of widely differing importance to patients, the number of events in its component of greater importance is small, or if the magnitude of effects differs markedly across its components<sup>4</sup>.

Utility scores may be used to explore the extent to which components of composite outcomes in randomized controlled trials vary in importance to patients. In a systematic review of cardiovascular trials published in 2002-2003, Ferreira-Gonzalez and collaborators first developed a hierarchical categorization of importance to patients for the components end points included in the eligible studies<sup>5</sup>. Published estimates of utility associated with the outcomes guided this process<sup>6</sup>. Five categories were hence created (Table 2): death, critical, major, moderate and minor.

*Table 2. Component outcomes by category of importance to patients*

<b>End point</b>	<b>Utility score (from Tengs and Wallace)</b>
<b>I. Death</b>	0.0
All cause mortality	
Mortality not otherwise defined	
Cardiac death not otherwise defined	
Cardiac death due to coronary heart disease not otherwise defined	
<b>II. Critical</b>	0.7 – 0.8
Large myocardial infarction	
Stroke leaving permanent moderate deficit	
Cardiac arrest followed by resuscitation manoeuvres	
Dissecting or ruptured aortic aneurysm	
<b>III. Major</b>	0.8 – 0.9
Non-fatal myocardial infarction	

<sup>3</sup> Meinert CL. Clinical trials dictionary. Baltimore : the Johns Hopkins Center for Clinical Trials; 1996.

<sup>4</sup> Montori VM, Permyer-Miranda G, Ferreira-Gonzalez I, et al. Validity of composite end points in clinical trials. BMJ 2005; 330: 594-6.

<sup>5</sup> Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, et al. Problems with the use of composite endpoints in cardiovascular trials: systematic review of randomised controlled trials. BMJ. 2007; 334: 786.

<sup>6</sup> Tengs TO, Wallace A. One thousand health-related quality of life estimates. Med Care 2000; 38: 583-637.

Stroke leaving permanent deficit, severity not defined

Coronary artery bypass grafting

Cerebrovascular event not otherwise defined

#### IV. Moderate

0.9 – 0.95

Coronary revascularisation not otherwise specified

Coronary revascularisation—angioplasty/stenting

Non-fatal angina needing hospital admission

Hospital admission not otherwise specified

#### V. Minor

Non-fatal angina, not defined

> 0.95

Non-fatal arrhythmias, not otherwise specified

Dyspnoea, not otherwise defined

Change in blood pressure

To describe the gradient of importance to patients among the components end points, Ferreira-Gonzalez and collaborators considered a large gradient to be present if the composite outcome combined outcomes from categories I or II (fatal or critical) with outcomes from category V (minor). They considered a moderate gradient to be present if the composite outcome combined outcomes from categories I or II (fatal or critical) with outcomes from category IV (moderate). They assigned a minor (or absent) gradient to composite outcomes not included in the other two categories. From 114 trials, only 14 (12%) included a composite outcome with either no gradient or minor gradient in importance to patients. The pooled treatment effects of interventions on fatal and critical outcomes were similar. The authors concluded that confident interpretation of composite outcomes requires small gradients of importance to patients and similar risk reduction across components.

**Conclusion:** From this scheme of categorization and from the results of our study, the prescription of CONT-O2 would therefore be classified as “critical”. The gradient of importance to patients between death and prescription of LTOT is minor. The composite of death and requirement for CONT-O2 is appropriate.

## APPENDIX 6

### SYSTEMATIC REVIEW AND META-ANALYSIS OF NOCTURNAL OXYGEN THERAPY IN COPD

**Yves Lacasse, Sylvie Martin.** *Centre de recherche, Centre de Pneumologie, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie de l'Université Laval, Québec, Canada*

**Background:** A systematic review / meta-analysis of domiciliary oxygen in COPD was published in 2005 in the Cochrane Library<sup>[7]</sup>. In this review, the studies of continuous oxygen therapy (provided for at least 15 hours per day) were considered separately from those of nocturnal oxygen therapy alone. Only 2 small randomized controlled trials of nocturnal oxygen therapy were uncovered. The analysis was limited to the outcome of mortality. Almost four years have elapsed since the publication of this meta-analysis.

**Objectives: General objective:** To update/expand Cranston's systematic review and meta-analysis of nocturnal oxygen therapy in COPD.

**Specific objectives:** (1) to locate any additional unpublished or ongoing trial on nocturnal oxygen therapy in COPD; (2) to determine the effect of nocturnal oxygen therapy on survival and disease progression in patients with COPD.

**Methods: Search strategy:** We accessed, in January 2009, the Cochrane Library with the following search strategy: ((Oxygen\* or O2) and (home\* or domicil\* or long-term or "long term")) or LTOT. The Medline, Embase and CINHALL databases were also reviewed using these search words: «"nocturnal oxygen therapy" [all fields]» from 2005 to 2009. Lastly, we hand-searched the 2005, 2006, 2007, and 2008 American Thoracic Society, American College of Chest Physicians and European Respiratory Society meeting abstracts.

**Selection criteria:** Two reviewers (YL and SM) independently assessed the titles and abstracts of all citations obtained to only select randomized controlled trials of nocturnal oxygen therapy in patients with COPD. Control groups received either conventional care or any other nocturnal therapy. If the title of an article and its abstract suggested any possibility that it might be relevant, the paper was retrieved and independently assessed by the same reviewers for a final decision about its inclusion into the meta-analysis.

**Data collection and analysis:** Pooled statistics were calculated as Peto Odds Ratios with 95% confidence intervals (CI).

**Results: Literature search** (Figure): 986 separate publications were retrieved. Both reviewers located and agreed to include only the same 2 randomized trials retrieved by Cranston et al.<sup>[7]</sup>. These two trials compared nocturnal oxygen therapy to usual care; one was an open trial<sup>[8]</sup> whereas the other was placebo-controlled<sup>[9]</sup>. The agreement between the reviewers was substantial (quadratic weighted Kappa: 0.77; 95% CI: 0.45 – 0.80).

**Effects of nocturnal oxygen therapy on mortality and disease progression:** In the meta-analysis, there was no difference in mortality between the treated and the control groups. Considering mortality as the only outcome, the pooled odds ratio was 0.97 (95% CI: 0.41 – 2.31;  $p_{\text{homogeneity}} = 0.69$ ). Also, we expanded Cranston et al.'s review by conducting a meta-analysis of the composite outcome (i.e.,

<sup>7</sup> Cranston JM, Crockett AJ, Moss JR, et al. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005; Oct 19; CD001744.

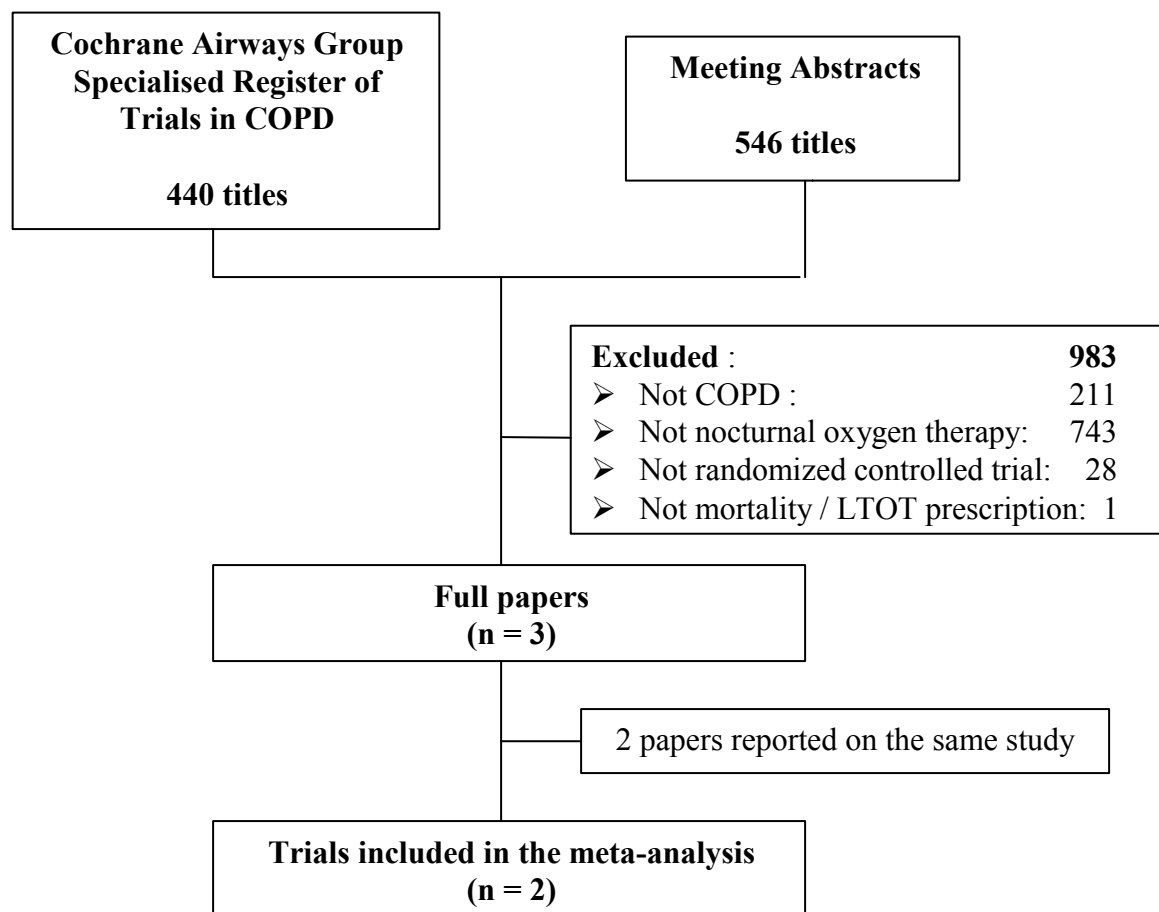
<sup>8</sup> Chaouat A, Weitzenblum E, Kessler R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J 1999; 14: 1002-8.

<sup>9</sup> Fletcher EC, Luckett RA, Goodnight-White S, et al. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO<sub>2</sub> above 60 mm Hg. Am Rev Respir Dis 1992; 145: 1070-76.

mortality or requirement for continuous oxygen therapy, a marker of disease progression). There was no difference in the composite outcome between the treated and the control groups (pooled odds ratio was 1.57 [95% CI: 0.75 – 3.26];  $p_{\text{homogeneity}} = 0.47$ ).

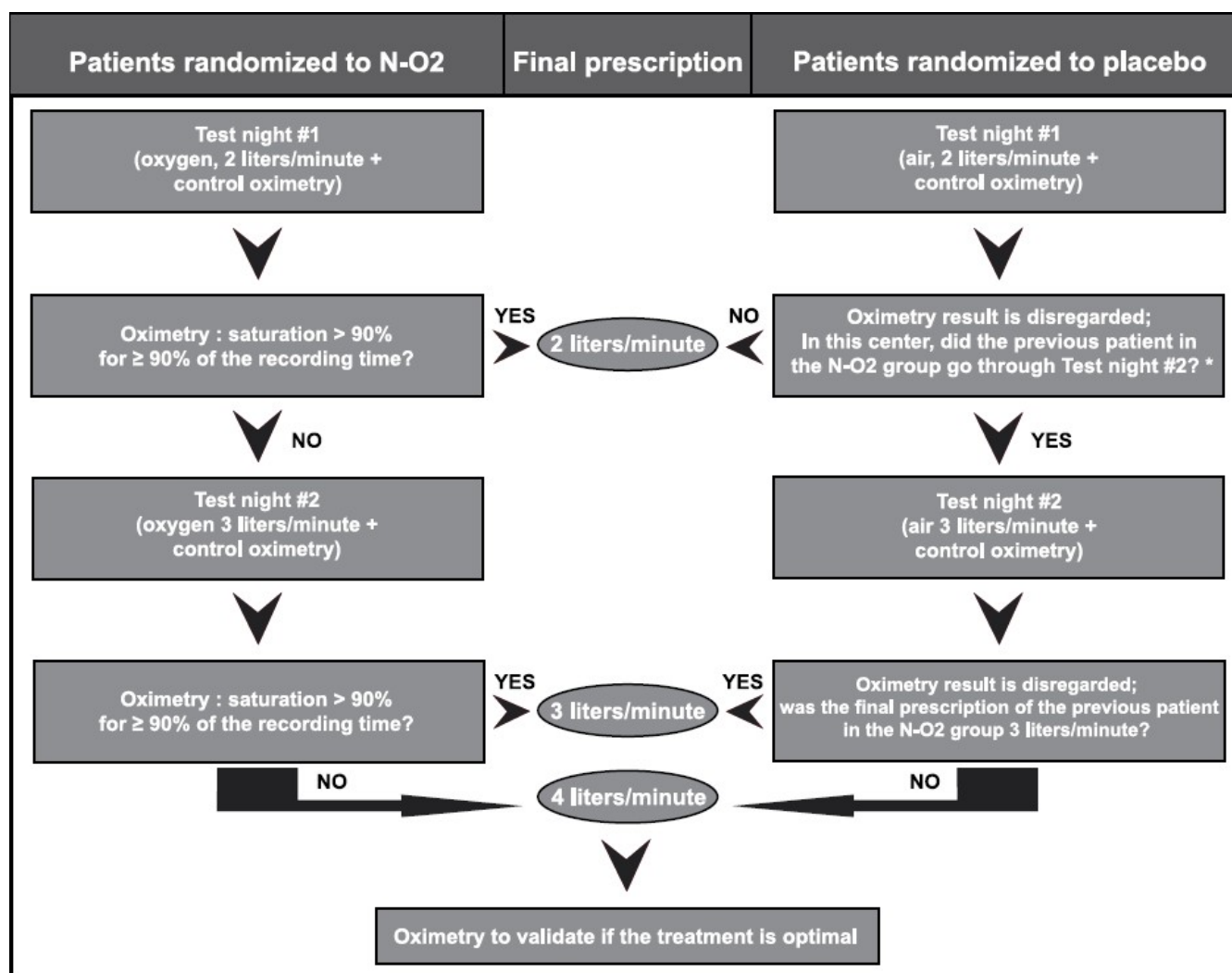
**Conclusions:** Current evidence in the literature does not support the prescription of nocturnal oxygen therapy to improve survival or slow down disease progression in patients with COPD. However, the confidence intervals around the pooled treatment effects are wide, and clinically significant effects are plausible. More research is needed.

**Figure: Study selection**



## APPENDIX 7

### OXYGEN (OR PLACEBO) TITRATION PROCESS



\* At this point of the trial, if no patient is randomized to N-O2, then the final prescription is by default 2 liters/minute, without further testing.

## APPENDIX 8

### LETTER OF AGREEMENT- LABORATOIRE DE TÉLÉMATIQUE



**RSR**  
Réseau en Santé  
Respiratoire du FRSQ

**DIRECTEUR**  
**Dr Yves Berthiaume**  
Centre de recherche, pavillon Masson  
Hôtel Dieu de Montréal  
3850 Saint-Urbain  
Montréal, Qc H2W 1T5  
Téléphone: (514) 890 8000 post 12922  
Télécopieur: (514) 4127204  
yves.berthiaume@umontreal.ca

**DIRECTEUR-ADJOINT**  
**Dr Basil Petrof**

#### REGROUPEMENTS STRATÉGIQUES

**Apnée obstructive du sommeil et  
facteurs de morbidité  
cardiovasculaires**  
**Dr Frédéric Sénes**

**Asthme et obésité**  
**Dr Louis Philippe Boivin**

**Bioaérosols et santé respiratoire**  
**Dr Caroline Duchaine**

**Fibrose kystique**  
**Dr André Cantin**

**Infections respiratoires et virus  
émergents**  
**Dr Guy Boivin**

**Soins critiques respiratoires**  
**Dr Philippe Juvet**

**Maladies pulmonaires obstructives  
chroniques**  
**Dr Jean Bourbeau**

#### INFRASTRUCTURES

**Banque de tissus**  
**Dr Michel Laviolette**

**Laboratoire de Télémétrie  
Biomédicale**  
**Dr Eric Rousseau**

**Plateforme génomique**  
**Dr Catherine Laprise**

**Cellule éthique**  
**Dr Bruno Awissi**

**Formation**  
**Dr Yvon Cormier**

**DIRECTEUR ADMINISTRATIF**  
**Dr Bruno Awissi**  
Unité d'épidémiologie respiratoire  
Université McGill  
3650 Saint-Urbain  
Montréal, Qc H2X 2P4  
Téléphone: (514) 843 2210  
Télécopieur: (514) 843 2083  
Courriel: bruno.awissi@mcgill.ca

**SITE WEB**  
<http://www.rsr.chus.qc.ca>

Sherbrooke, le 24 Janvier 2009.

**Dr Yves Lacasse**  
Pneumologue  
Hôpital Laval, Québec

Bonjour Dr Lacasse,

Nous avons évalué le temps requis pour réaliser votre projet " Multi-center randomized placebo-controlled trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease" (CANOX) et avec ce que nous avons comme information, un délai de 16 semaines de travail serait requis. Le document d'analyse sommaire est allié.

Au tarif de notre analyste-programmeur actuel, la portion à budgéter pour la programmation de l'application serait :

16 semaines à 35 heures/semaines = 560 heures  
560 heures à 24,70 \$/heure = 13 832,00 \$  
à ceci s'ajoute les avantages sociaux et autres bénéfices marginaux (2904,72 \$),  
soit un total de **16 736,72.00 \$**

Tel que mentionné dans votre message, l'ajout de fonctionnalités tel que le "Serious adverse events module" et le "Arborescent screening log" n'est pas compris dans cette estimation. Pour ces modules supplémentaires, il faudrait compter une somme de **4000 \$**.

De plus, il faut prévoir des frais de **1000 \$** qui se détaillent comme suit:

- 1- un tarif annuel récurrent pour l'hébergement sécurisé de l'application d'environ 150.00 \$ par année sur le serveur du réseau.
- 2- des frais de déplacement en début et fin de projet pour notre analyste-programmeur de l'ordre de 450 \$
- 3- des frais pour l'extraction des données en fin de projet de l'ordre de 400 \$

Pour un grand total estimé à **21736,72 \$**

En espérant le tout conforme à vos attentes. Cordialement vôtre.

**Eric Rousseau**  
Laboratoire de Télémétrie Biomédicale  
Réseau en Santé Respiratoire du FRSQ  
819 564-5306



## APPENDIX 9

### LETTER OF SUPPORT OF THE CANADIAN RESPIRATORY CLINICAL RESEARCH CONSORTIUM



February 3, 2009

Yves Lacasse  
Centre de pneumologie  
Hôpital Laval  
2725 Chemin Ste-Foy  
Ste-Foy, P. Québec  
G1V 4G5  
Fax: 418-656-4762

Dear Yves,

On behalf of the Canadian Respiratory Clinical Research Consortium it is my pleasure to write a letter of support for your clinical trial entitled: Multi-center randomized placebo-controlled trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease.

Your study protocol was presented to our group at our Winter 2005 symposium and it was very well received. In the meantime, you have continued to refine your protocol and complete several pilot studies which have demonstrated the relevance of the question to Canadian public health, as well as the feasibility of the ultimate clinical trial.

The Canadian Respiratory Clinical Research Consortium (CRCRC), under the leadership of the Canadian Lung Association's Canadian Thoracic Society's clinical trials committee, is an umbrella organization of professional societies with a special interest in respiratory related clinical research. The Consortium functions as a not for profit organization and is independent of industry. Representatives from all of Canada's teaching centers are members of the consortium. Our consortium was developed to promote clinical research that answers important questions arising in adult and pediatric pulmonary medicine. The Consortium places particular emphasis on studies needed to increase or establish the level of evidence of key recommendations of treatment guidelines.

We have chosen to support your trial as an important one that we would particularly like to be involved with. Our network of respiratory researchers across Canada is keen to be involved in this study, and our members are committed towards recruiting patients for your study. We wish you success with your CIHR grant application. This will be an exciting opportunity for a cross-Canada collaborative effort to better the lives of patients affected by COPD.

Sincerely,

Shawn Aaron, MD, MSc, FRCPC  
Chairman, CRCRC

## **APPENDIX 10**

### **CO-INVESTIGATORS AND COLLABORATORS**

#### **New Brunswick, Canada**

Dr. Marcel Mallet, Dr.-Georges-L.-Dumont University Hospital Centre, Moncton

#### **Quebec, Canada**

Dr. Jean Bourbeau, Montreal Chest Institute, Montreal

Dr. Bruno Paradis, CSSS de Laval – Centre ambulatoire, Laval

Dr. François Maltais, Institut universitaire de cardiologie et de pneumologie de Québec, Québec

Dr. Richard Lecours, Hôtel-Dieu de Lévis, Lévis

Dr. Pierre Larivée, Centre hospitalier universitaire de Sherbrooke, Sherbrooke

Dr. Marc Baltzan, Mount Sinai Hospital, Montreal

Dr. Christine Drapeau, Centre hospitalier régional de Trois-Rivières, Trois-Rivières

Dr. Guy Cournoyer, Hôpital régional de Saint-Jérôme, Saint-Jérôme

#### **Ontario, Canada**

Dr. Shawn Aaron, The Ottawa Hospital – General Campus, Ottawa

Dr. Denis O'Donnell, Kingston General Hospital, Kingston

#### **Manitoba, Canada**

Dr. Martha Sheperdtecky, St. Boniface General Hospital, Winnipeg

#### **Alberta, Canada**

Dr. Eric Wong, University of Alberta Hospital, Edmonton

#### **British Columbia, Canada**

Dr. Jeremy Road, Vancouver General Hospital, University of British Columbia, Vancouver

#### **Portugal**

Dr. Paula Simão, Hospital Pedro Hispano, Matosinhos

Dr. Miguel Guimarães, Centro Hospitalar Vila Nova de Gaia / Espinho EPE, Vila Nova de Gaia

Dr. Cristina Bárbara and Dr. Paula Pinto, Hospital Pulido Valente, CH de Lisboa Norte, Lisboa

Dr. Joaquim Moita, Centro Hospitalar de Coimbra, Quinta dos Vales, Coimbra

Dr. João Munhá, Centro Hospitalar do Barlavento Algarvio – EPE, Portimão

Dr. Salette Valente, Centro Hospitalar Cova da Beira, Covilhã

#### **France**

Dr. Jean-Claude Meurice, CHU de Poitiers, Poitiers

Dr. Alain Palot and Dr. Pascal Chanez, Hôpital Nord, Marseille

Dr. Jésus Gonzalez, Groupe Hospitalier Pitié Salpêtrière, Paris

#### **Spain**

Dr. Carlos Javier Egea Santaolalla, Hospital Txagorritxu, Vitoria-Gasteiz

Dr. Araceli Abad Fernández, Hospital Universitario de Getafe, Getafe

Dr. Javier Sayas Catalán, Hospital Universitario 12 de Octubre, Madrid

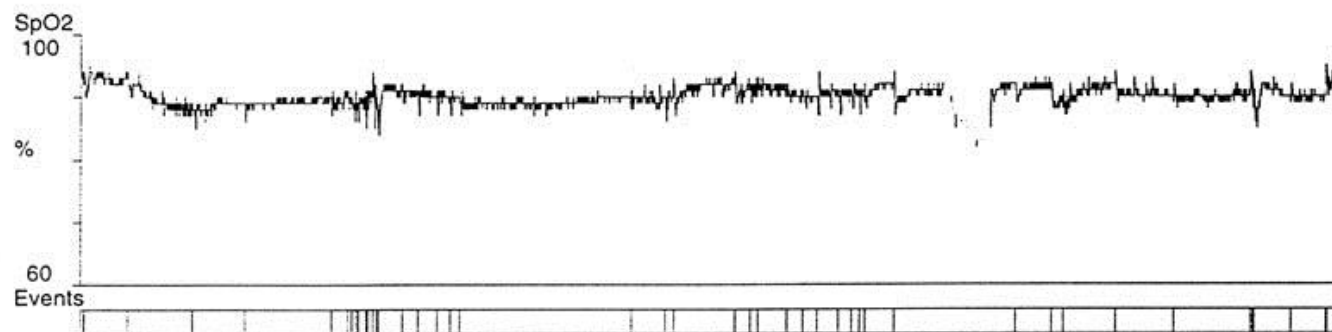
Dr. Cristóbal Esteban, Hospital Galdakao-Usansolo, Galdakao

## APPENDIX 11

### NOCTURNAL OXIMETRY TRACINGS IN PATIENTS WITH COPD NOT QUALIFYING FOR CONTINUOUS OXYGEN THERAPY

- (A) Nocturnal oxygen desaturation (> 30% of the recording time with a saturation < 90%) with non-periodic variation in saturation throughout sleep. This tracing is not suggestive of sleep apnea.

Graphic Summary



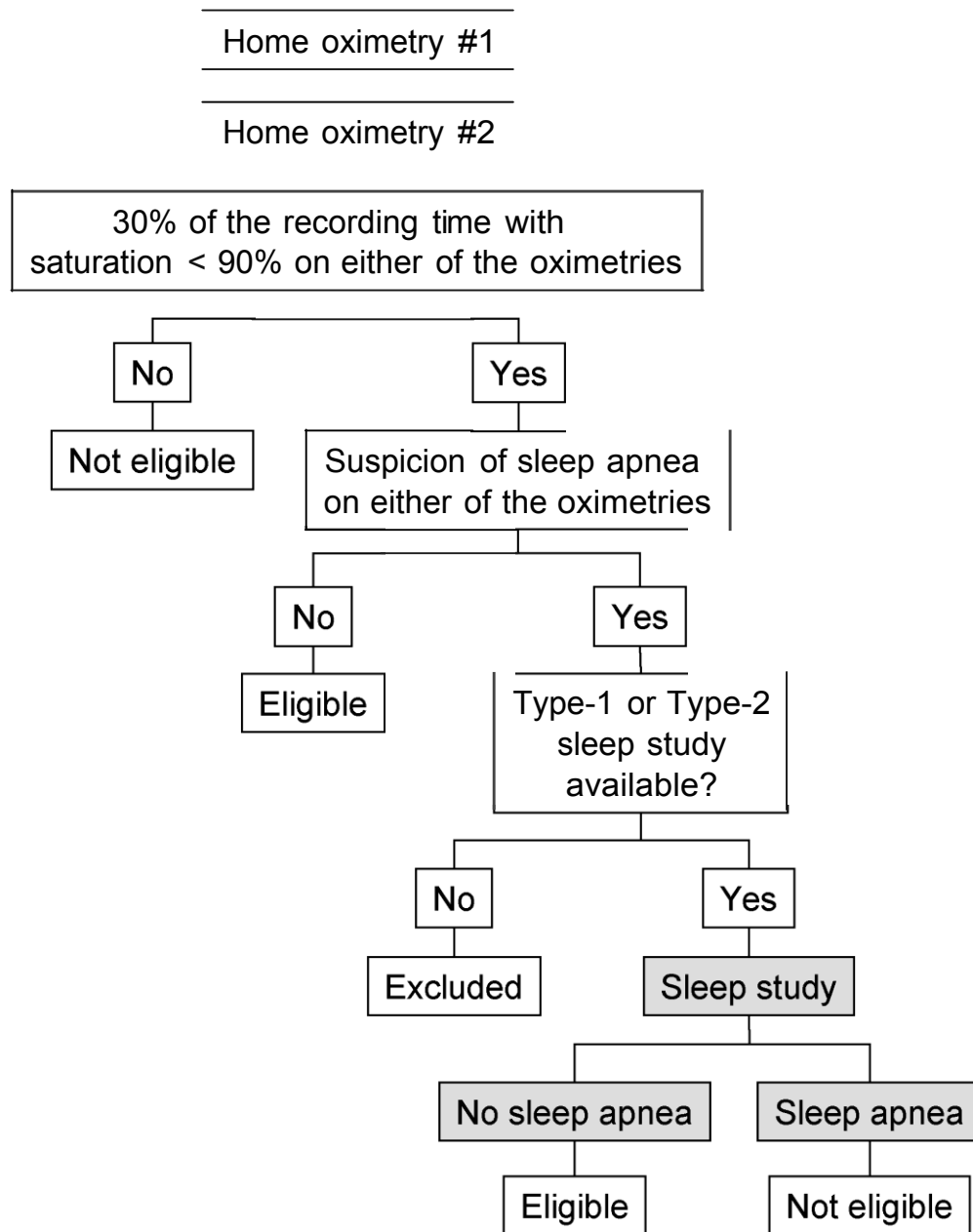
- (B) Nocturnal oxygen desaturation with cyclical changes in saturation suggesting sleep apnea.

Graphic Summary



## APPENDIX 12

### PATIENT SCREENING: DIAGNOSIS OF NOCTURNAL DESATURATION <sup>1</sup>



<sup>1</sup>Shaded boxes: procedures performed off-protocol (see protocol, section 2.5.4 *Nocturnal desaturation: operational definition and patient selection*).

**APPENDIX 13****AMERICAN ACADEMY OF SLEEP MEDICINE CLASSIFICATION SYSTEM FOR SLEEP APNEA EVALUATION STUDIES<sup>[1]</sup>**

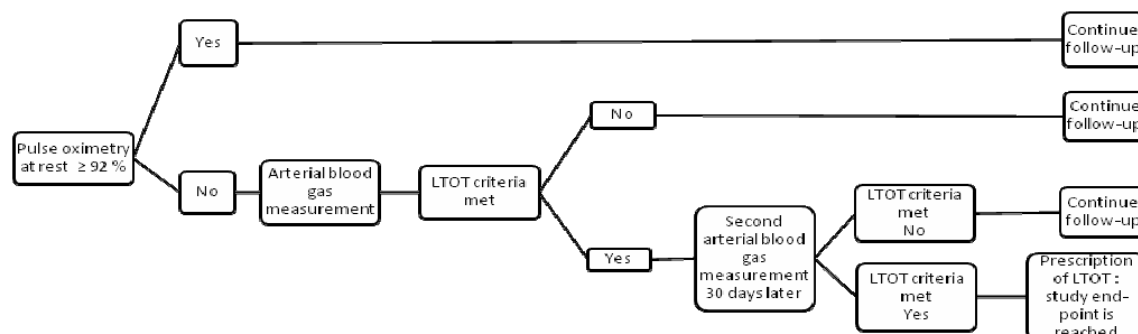
	Type 1: standard polysomnography	Type 2: comprehensive portable polysomnography	Type 3: modified portable sleep apnea testing	Type 4: continuous single or dual parameter recording
Parameters	Minimum of 7, including EEG, EOG, chin EMG, ECG, airflow respiratory effort, O2 saturation	Minimum of 7, including EEG, EOG, chin EMG, ECG, airflow respiratory effort, O2 saturation	Minimum of 4, including ventilation, heart rate or ECG, O2 saturation	Minimum of 1: O2 saturation, flow, or chest movement
Body position	Documented or objectively measured	Possible	Possible	No
Leg movement	EMG or motion sensor desirable but optional	Optional	Optional	No
Personnel in attendance	Yes	No	No	No
Interventions during the study	Possible	No	No	No

EEG: electroencephalography; EOG: electrooculography; EMG: electromyography; ECG: electrocardiography.

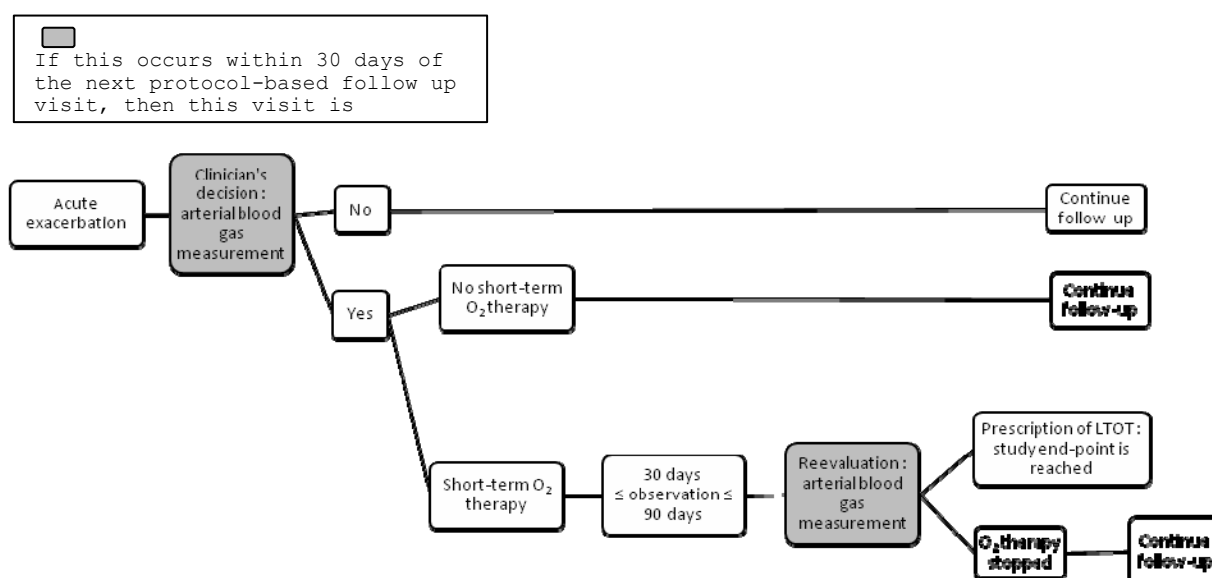
<sup>1</sup> American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999; 22: 667-89.

## APPENDIX 14

### A) Prescription of long-term oxygen therapy in stable patients (patients evaluated during a regular follow up visit)



### B) Prescription of long-term oxygen therapy in unstable patients (patients evaluated outside of the regular follow up visits, most likely in the course of an acute exacerbation)



## **APPENDIX 15**

### **INOX' CASE REPORT FORM**

## APPENDIX 16

### SAMPLE SIZE

#### 1. Sample size requirements for secondary outcome analyses

Disease-specific quality of life is the secondary outcome of this trial. Disease-specific quality of life will be measured using the St. George's Respiratory Questionnaire, an instrument that has been extensively validated in patients with all grades of respiratory disease including advanced COPD. The questionnaire consists of 76 items divided into three domains (symptoms, activity, and impact). Scores range from zero (perfect health) to 100 (worst possible) for each component; a total score which summarizes the responses to all items is obtained. A change in score of 4 units may be considered clinically significant.

Disease-specific quality of life will be measured in 27 selected centers with specific facilities and expertise. To decide on the number of selected centers and the target sample size in each of them, we computed the total sample size needed to give 80% chance of showing a statistically significant difference in SGRQ scores between two study periods, at a two-sided significance level of 5%, if the true benefit of N-O<sub>2</sub> reaches the minimal clinically important difference (4 units on a 100-point scale<sup>[1,2]</sup>). We derived baseline scores (and standard deviations) from 6 randomized trials of respiratory rehabilitation in COPD<sup>[3,4,5,6,7,8]</sup> that enrolled patients whose baseline demographic and clinical characteristics were very similar to those who will meet the inclusion criteria of our trial. In these randomized trials, baseline standard deviations were remarkably homogeneous (pooled SD: 14.74)<sup>[9]</sup>. From these specifications, we determined that 213 patients per group (total: 426) are needed, which is much smaller than the target sample size in the primary outcome analysis.

#### 2. Sample size requirements for economic analyses

The objective of the INOX trial is not to demonstrate superiority of either of the treatment arm in terms of cost-effectiveness. Rather, a secondary objective of the trial is to determine the cost-effectiveness ratio of nocturnal oxygen therapy over a 3-year period. Non-parametric analyses (i.e., bootstrapping) will be used to derive confidence intervals for the incremental cost effectiveness ratio (see section 2.16.2).

---

<sup>1</sup> Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; 19: 398-404.

<sup>2</sup> Schunemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. *J Clin Epidemiol* 2003; 56: 1170-6.

<sup>3</sup> Engström CP, Persson LO, Larsson S, Sullivan M. Long-term effects of a pulmonary rehabilitation programme in outpatients with chronic obstructive pulmonary disease: A randomized controlled study. *Scandinavian Journal of Rehabilitation Medicine* 1999; 31: 207-13.

<sup>4</sup> Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomized controlled trial. *The Lancet* 2000; 355: 362-8.

<sup>5</sup> Boxall A, Barclay L, Caplan G. A randomized controlled trial of home-based pulmonary rehabilitation for elderly, housebound COPD patients. In: *Proceedings of the Thoracic Society of Australia & New Zealand, Annual Scientific Meeting, Adelaide, 4-9 April. 2003: P106.*

<sup>6</sup> Finnerty JP, Keeping I, Bullough I, Jones J. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease. A randomized controlled trial. *Chest* 2001; 119: 1705-10.

<sup>7</sup> Ringbaek TJ, Broendum E, Hemmingsen L, Lybeck K, Nielsen D, Andersen C, et al. Rehabilitation of patients with chronic obstructive pulmonary disease. Exercise twice a week is not sufficient!. *Respiratory Medicine* 2000; 94: 150-4.

<sup>8</sup> Chlumsky J, Sterbova L, Smolikova L, Matous M, Salajka F. The effect of pulmonary rehabilitation on exercise tolerance and quality of life in patients with COPD. Preliminary data. *Eur Respir J* 2001; 18:223s.

<sup>9</sup> Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD003793.pub2. DOI: 10.1002/14651858.CD003793.pub2.



## **APPENDIX 17**

### **CHARTER FOR DATA MONITORING COMMITTEE**

#### **1. INTRODUCTION**

The International Nocturnal Oxygen (INOX) trial is a multi-centre randomized placebo-controlled trial of nocturnal oxygen therapy in patients with COPD that is funded by the Canadian Institutes for Health Research. The INOX is registered at the U.S. National Institutes of Health (ClinicalTrials.gov – NCT01044628) and at the International Standard Randomised Controlled Trial Number (ISRCTN) Register (ISRCTN50085100).

The objective of the INOX trial is to determine, in patients with chronic obstructive pulmonary disease (COPD) not qualifying for long-term oxygen therapy (LTOT) who exhibit significant nocturnal arterial oxygen desaturation, whether nocturnal oxygen therapy provided for a period of 3 years decreases mortality or delay the requirement for LTOT. A secondary objective of the trial is to determine the cost-utility ratio of nocturnal oxygen therapy over a 3-year period.

*The purpose of this document is to describe the roles and responsibilities of the independent Data Monitoring Committee (DMC) for the INOX trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.*

#### **2. ROLES AND RESPONSIBILITIES**

##### **2.1 Aims of the committee**

- To assist and advise the Steering Committee so as to protect the validity and credibility of the trial.
- To safeguard the interests of trial participants by assessing the safety and efficacy of the interventions during the trial.
- To monitor the overall conduct of the clinical trial.

##### **2.2 Terms of reference**

- The DMC receives and reviews the progress and accruing data of the trial and provides advice on the conduct of the trial to the Steering Committee.
- The DMC informs the Chair of the Steering committee if, in their view:
  - (i) the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated; **or**
  - (ii) it becomes evident that no clear outcome would be obtained.

##### **2.3 Specific roles of DMC**

- To advise on protocol modifications suggested by the Steering Committee (e.g., to inclusion criteria, trial endpoints, or sample size).
- To suggest additional data analyses.
- To review the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data.
- To monitor:
  - recruitment figures and losses to follow-up;
  - compliance with the protocol by participants and investigators;
  - trial conduct – organization and implementation of trial protocol;
  - evidence for treatment differences in the main efficacy outcome measures;
  - evidence for treatment harm (e.g., toxicity data, serious adverse effects, deaths);
  - planned sample size assumptions;

- compliance with previous DMC recommendations.
- To assess the impact and relevance of external evidence.
- To decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups.

### **3. BEFORE OR EARLY IN THE TRIAL**

#### **3.1 Decision to join the DMC**

All potential DMC members shall have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins, the trial will have undergone review by the funder, and local research ethics committee. Therefore, if a potential DMC member has major reservations about the trial (e.g., the protocol or the logistics), he/she should report these to the trial office and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

DMC members formally register their assent by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter.

#### **3.2 Meeting before the start of the trial**

The DMC met in Toronto on April 22, 2010 before the trial to discuss the protocol and to have the opportunity to clarify any aspects with the principal investigators.

### **4. COMPOSITION**

#### **4.1 Membership and size of the DMC**

The members of the DMC for this trial are Dr. James Brophy (Cardiology and Clinical epidemiology, McGill University), Dr. Nick Anthonisen (Respiratory medicine, University of Manitoba), and Dr. Robin Roberts (Biostatistics, McMaster University). All three have experience in data monitoring.

The members are independent of the trial. They have not been involved with the trial in any other way or have some competing interest that could impact on the trial. Any competing interests, both real and potential, should be declared. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. A competing interest form will be completed and returned by the DMC members to the trial coordinating centre.

#### **4.2 Responsibilities of the DMC's Chair**

The Chair should have previous experience of serving on DMCs and experience of chairing meetings, and should be able to facilitate and summarize discussions. The Chair is expected to facilitate and summarize discussions. During the first DMC meeting, the members designated Dr. James Brophy as the Chair of the committee.

#### **4.3 Responsibilities of the statisticians**

- The reports to the DMC will be produced by the “Service de consultation statistique” of Laval University. The trial statistician is independent from this service.
- The DMC's statistician (Dr. Robin Roberts) will not participate in the production of the reports to the DMC.
- The DMC's statistician will provide independent statistical expertise to further guide the other DMC members through the report.

#### **4.4 Responsibilities of the trial's office team**

The trial office team (e.g., Trial Manager, etc) will only input to the production of the non-confidential sections of the DMC report.

#### **4.5 Responsibilities of the Principal investigator (PI) and Steering Committee**

The PI, may be asked, and should be available, to attend open sessions of the DMC meeting. The other

Steering Committee's members will not usually be expected to attend but can attend open sessions when necessary.

#### **4. 6. Final decisions: Relationships between the DMC and the Steering Committee**

The DMC does not make decisions about the trial, but rather makes recommendations to the Steering Committee.

### **5. ORGANIZATION OF DMC MEETINGS**

#### **5.1 Frequency**

The exact frequency of meetings will depend upon any statistical plans specified, and otherwise on trial events. The wishes of the DMC and needs of the trial office will be considered when planning each meeting.

#### **5.2 Setting**

The first meeting will be face-to-face to facilitate full discussion and allow members to get to know each other. Depending on the composition of the DMC, all subsequent meetings will be face-to-face if possible, with teleconference as a second option.

#### **5.3 Open and closed sessions**

A mixture of open and closed sessions will take place. Only DMC members and others whom they specifically invite (e.g., the trial statistician), will be present in closed sessions. In open sessions, all those attending the closed session will be joined by the principal investigator and/or any member of the Steering committee.

### **6. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY**

#### **6.1 Material available**

During the first DMC meeting, the members decided to be unblinded to the allocation group throughout the trial. Accordingly, all sessions will be open. Therefore, the material will include efficacy and safety data by allocation group.

- Open sessions: Accumulating information relating performance standards (recruitment and data quality) will be presented. This information will include screening logs, treatment compliance data, and data return rates). . Toxicity details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.
- Closed sessions: In addition to all the material available in the open session, the closed session material will include efficacy and safety data by coded allocation group.
- The DMC members will receive the report at least 2 weeks before any meetings.

#### **6.2 Blinding**

The members of the DMC will decide whether they wish to be blinded or not to the allocation groups. During the first DMC meeting, the members decided to be unblinded to the allocation group throughout the trial.

#### **6.3 Confidentiality**

- DMC members do not have the right to share confidential information with anyone outside the DMC, including the PI.
- The DMC members should destroy their reports after each meetings. Fresh copies of previous reports will be circulated with the newest report before each meeting.

#### **6.4 Documentation**

The principal investigator or the trials office team will collate any such information and provide it to the DMC members. Identification of external evidence (e.g., from other trials/ systematic reviews) is not the responsibility of the DMC members.

## **7. DECISION MAKING**

### **7.1 Possible recommendations**

Possible recommendations of the DMC could include:

- No action needed, trial continues as planned;
- Early stopping due, for example, to clear benefit or harm of a treatment, , or external evidence;
- Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up;
- Sanctioning and/or proposing protocol changes.

### **7.2 Interim analysis schedule and procedures**

During its first meeting, the DMC members will finalize an interim analysis plan (schedule and rules). The Steering committee suggests that:

- only one interim analysis be conducted;
- for efficacy, the composite outcome of mortality or progression to continuous oxygen therapy be monitored using the sequence of nominal significance levels of 0.001 and 0.05 (two-sided) <sup>[1,2]</sup>;
- safety be monitored every 6 months or more frequently if requested by the DMC. Although no formal boundaries for safety monitoring are defined, clear evidence of net harm with no beneficial effect would be expected before the DMC recommends to terminate the trial.

### **7.3 Voting**

Every effort will be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be included in the report to the Steering committee as these may inappropriately convey information about the state of the trial data.

### **7.4 Quorum**

Effort should be made for all members to attend. The trials office team will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair, will be present. If the DMC is considering recommending major action after a meeting, the DMC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC.

### **7.5 Attendance**

If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.

## **8. REPORTING**

### **8.1 Communication of the decisions**

The DMC will report its recommendations in writing to Principal investigator within 24 hours. The Steering Committee will be notified of any correspondence between the DMC and the Principal investigator within 2 weeks.

### **8.2 Disagreement**

If the DMC has serious problems or concerns with the Steering committee decision, a meeting of these groups will be held. The information to be shown will depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement, confidential data may have to be revealed to all those attending such a meeting. The meeting will be chaired by an external expert who is not directly involved with the trial.

## **9. AFTER THE TRIAL**

### **9.1 Final meeting**

At the end of the trial, there will be a meeting to allow the DMC to discuss the final data with the Steering committee and give advice about data interpretation.

### **9.2 Publication**

DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. During the first DMC meeting, the members agreed that neither their name nor their affiliations will be listed in the main report.

A brief summary of the timings and conclusions of DMC meetings will be included in the body of this paper.

The DMC will be given the opportunity to read and comment on any publications before submission.